# Sertraline Treatment for Generalized Anxiety Disorder: A Randomized, Double-Blind, Placebo-Controlled Study

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***Objective:*** This study assessed the efficacy and safety of sertraline in the treatment of generalized anxiety disorder (GAD).

***Method:*** The study was conducted from April 2000 to May 2002. Outpatients with DSM-IV GAD (N = 326) who satisfied inclusion/exclusion criteria and completed a 1-week screening phase were randomly assigned to 10-week double-blind treatment with flexible dosing of sertraline (50–200 mg/day) or placebo. The primary efficacy measure was change from baseline in Hamilton Rating Scale for Anxiety (HAM-A) total score. Response was defined as a 50% or greater decrease in HAM-A total score at endpoint.

***Results:*** Sertraline produced a statistically significant reduction in anxiety symptoms, as measured by HAM-A total change scores ($p = .032$), HAM-A psychic anxiety subscale ($p = .011$), and Hospital Anxiety and Depression Scale-anxiety subscale ($p = .001$). Response rates were significantly higher ($p = .05$) for the sertraline group (59.2%) compared to the placebo group (48.2%). Sertraline was well tolerated, with only sexual side effects reported significantly more often by subjects receiving sertraline than those receiving placebo.

***Conclusion:*** Despite the relatively small between-group differences, study findings suggest a role for sertraline in the acute treatment of GAD.

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Generalized anxiety disorder (GAD) is characterized by excessive and uncontrollable anxiety and worry that are associated with symptoms of restlessness, irritability, insomnia, fatigue, difficulty concentrating, and muscle tension. There is now ample evidence indicating that GAD is a common, serious, and chronic illness that confers a level of functional impairment comparable to that in major depression.[1–4]

In recent years, trials using the selective serotonin reuptake inhibitors (SSRIs) paroxetine[5,6] and escitalopram[7] as well as the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine extended release[8,9] have established their efficacy in the treatment of GAD symptoms. The SSRI sertraline has been used effectively in the treatment of different anxiety disorders, including social anxiety disorder, posttraumatic stress disorder, panic disorder, and obsessive-compulsive disorder, and has shown potential efficacy in children and adolescents with GAD.[10,11] To date, 2 large, multicenter, placebo-controlled trials have been conducted in order to evaluate the efficacy and safety of sertraline in the treatment of subjects diagnosed with GAD. The first, a recently published trial by Allgulander and colleagues,[12] has shown sertraline to be effective in the treatment of adults with GAD. We report here the results of the second trial evaluating the efficacy of sertraline in GAD patients.

## METHOD

This double-blind, placebo-controlled study was conducted by 9 collaborating centers in the United States, with the Medical University of South Carolina (Charleston, S.C.) as the coordinating and lead site. The study was approved by the appropriate review boards at each of the participating centers. The benefits and risks of study participation were fully explained to each subject, and written informed consent was obtained. The study was conducted from April 2000 to May 2002.

### Patients

Eligible participants were male and female outpatients, 18 years and older, recruited through the media or local referrals, who met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)[13] criteria for

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a primary diagnosis of GAD as determined by study psychiatrists, psychiatric nurse clinicians, and psychologists using the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Version (SCID-I/P).[14] Those with clinically significant hepatic or renal disease or any other acute or unstable medical conditions were excluded.

A total score of 20 or higher on the Hamilton Rating Scale for Anxiety (HAM-A),[15] a score of 2 or higher on item 1 of the HAM-A (anxious mood), and a Covi Anxiety Scale[16] total score higher than the Raskin Depression Scale[17] score were required. Participants who had a diagnosis of major depressive disorder, panic disorder (or 2 or more panic attacks in the past month), obsessive-compulsive disorder, posttraumatic stress disorder, or substance abuse or dependence disorder within 6 months of study entry were excluded. Subjects with a current or past history of bipolar disorder or any psychotic disorder were also excluded. Participants with additional DSM-IV Axis I disorders were excluded. However, participants with dysthymia or social anxiety disorder were allowed provided that GAD was the primary diagnosis. A score of 18 or higher on the Montgomery-Asberg Depression Rating Scale (MADRS)[18] constituted an exclusionary criterion as well. Participants taking other psychotropic medications within 2 weeks of baseline (except 5 weeks for fluoxetine), patients who received electroconvulsive therapy, and women of childbearing potential who did not use appropriate contraception were excluded. Other exclusionary criteria included regular benzodiazepine use within 30 days of baseline visit, failure to respond to previous SSRI treatment with a minimum effective dose for at least 4 weeks within the current episode, and initiation or ongoing cognitive behavioral therapy or other forms of psychotherapy for anxiety symptoms. All participants had to meet inclusion criteria at baseline.

### Study Design

The study was a randomized, placebo-controlled, double-blind, flexible-dose study designed to evaluate the efficacy and safety of sertraline in the treatment of subjects with a primary diagnosis of moderate to severe DSM-IV GAD. The design did not include a placebo run-in phase.

The study consisted of screening and baseline evaluations followed by 10-week, double-blind, parallel treatment with either sertraline or placebo and a 1-week taper period. A computerized randomization list, stratified by site, was generated by the Coordinating Center at the Medical University of South Carolina. Equal allocation of the 2 treatment groups was used with a block size of either 4 or 6 to ensure that masking was not compromised. The study drug was packaged and labeled accordingly and delivered to the sites by a central pharmacy. The list of Participant Study Numbers and corresponding Study Drug Code Numbers (randomization numbers) was maintained at each site. Subjects were assigned the next available unique Study Drug Code Number in consecutive order.

Subjects who entered the double-blind phase received sertraline at 25 mg/day (or matching placebo) for 1 week followed thereafter by a flexible daily dosing of sertraline at 50 to 200 mg daily (once daily) based on clinical response and tolerability. Dose titration included medication increases at 2, 3, 4, and 7 weeks by 50-mg increments up to a maximum of 200 mg/day of sertraline or matching placebo at the investigator's discretion. Dosage reduction was permitted at any time during the study, and only one subsequent increase was allowed thereafter.

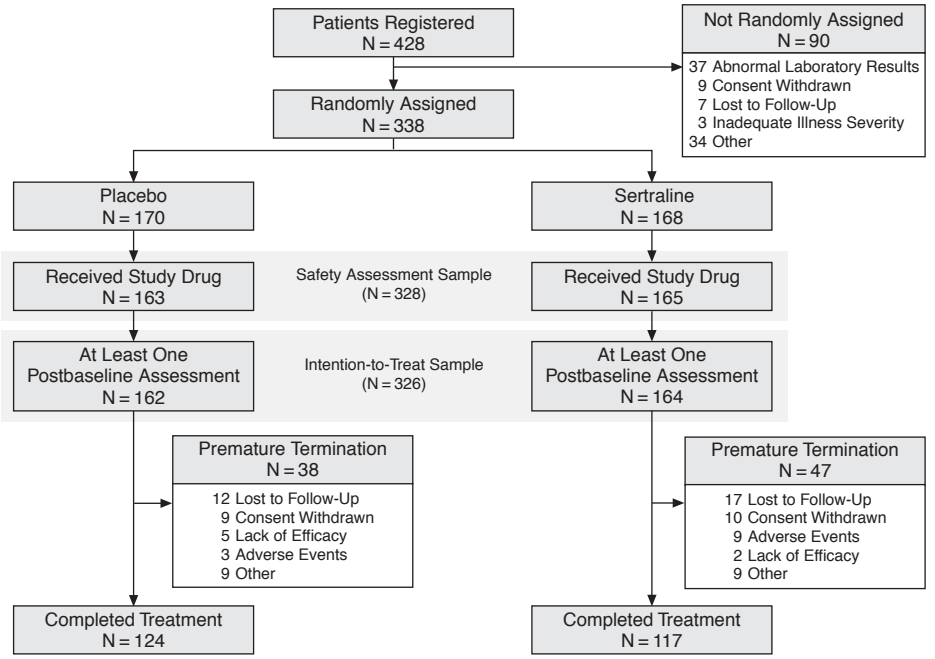
Study visits took place at screening (week –1), at baseline (week 0), and at the end of study weeks 1, 2, 3, 4, 6, 8, 10, and 11 (follow-up). All subjects randomly assigned in the trial continued their participation and study evaluations regardless of study medication and visit compliance or protocol violation status (including use of exclusionary concomitant medications or positive urine toxicology evaluation at week 4; N = 38). Participants were withdrawn from the study prior to completion only if necessitated due to adverse events or consent withdrawal.

### Efficacy Assessments

The primary outcome measure was the HAM-A[15] total score performed at every study visit. Secondary outcome measures included the patient-rated Hospital Anxiety and Depression Scale (HADS)[19] administered at every visit and the following clinician-rated measures: (1) HAM-A psychic and somatic subscales, (2) HAM-A items 1 (anxious mood) and 2 (tension) measuring fundamental GAD symptoms, and (3) the Clinical Global Impressions of Severity (CGI-S)[20] scale. Additional secondary outcome measures included the MADRS,[18] the Sheehan Disability Scale,[21] and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[22] administered at baseline and study end visits. Response was defined as a 50% or greater decrease from baseline in the HAM-A total score at endpoint. An additional response variable was defined as a score of 1 ("very much improved") or 2 ("much improved") on the global improvement rating of the CGI (CGI-I).[20]

Safety assessments included evaluation at each study visit of weight, sitting blood pressure, heart rate, and temperature. Adverse events were monitored throughout the study through spontaneous observation and report. The use of concomitant medications was recorded at each visit (comprehensive list of concomitant medications will be provided on request). A physical examination, an electrocardiogram, and laboratory assessments (clinical chemistry, hematology, urinalysis, pregnancy test) were completed at the screening visit and the study end (except urine toxicology screen performed at week 4).

Figure 1. Study Progress of Patients With Generalized Anxiety Disorder




Compliance was evaluated solely using a pill count of the returned study medication.

## Statistical Analyses

***Preliminary descriptive analyses.*** Continuous demographic (age) and baseline clinical (age at illness onset, CGI-S score, MADRS score, HAM-A total score) and mean daily dose at endpoint variables were compared for the sertraline and placebo groups using analysis of covariance with treatment group as the primary independent variable and clinical site as a covariate. Categorical demographic (gender, race) and clinical (percentage with prior psychiatric history, percentage with prior use of psychotropics) variables were compared using Cochran-Mantel-Haenszel $\chi^2$ with clinical site as a stratification variable. Distributional and other assumptions for proposed statistical methods were confirmed via blind preliminary analyses.

***Primary/secondary analyses.*** Primary and secondary efficacy analyses were carried out using the intention-to-treat (ITT) sample comprising all randomly assigned subjects who had at least 1 postbaseline measurement for the primary outcome variable. Change from baseline for continuous primary (HAM-A total score) and secondary outcome measures were compared for the sertraline and placebo groups using a longitudinal repeated-measures model with treatment, clinical site, visit, and visit-by-treatment interaction as fixed effects in the model. SAS PROC MIXED (SAS Institute Inc., Cary, N.C.) was used to account for the intrasubject correlation and subjects with intermittent missing outcome data. The best-fit covariance structure for each outcome variable, evaluated using Schwartz's Bayesian information criterion and Akaike information criterion, was found to be the unstructured covariance matrix. In addition to the main comparison of the overall longitudinal profile of outcome change scores over time (equivalent to tests of treatment differences in linear trends or slopes with time), treatment differences at each visit (change from baseline to each visit) were assessed using contrasts based on least squares (LS) means determined from the final model. In separate analyses, a differential relationship between treatment and outcome across clinical sites was investigated through use of a treatment-by-site interaction term in the statistical models. All site-by-treatment interaction effects were not statistically significant, and the site interaction term was not incorporated in the final models. The analyses used, as a basis for inference, the restricted maximum likelihood approach and Satterthwaite's approximation for estimating degrees of freedom for approximate F and t tests. Treatment effects sizes were estimated via 95% confidence interval estimates of the difference in LS means at study end based on the final model.

As a primary analysis for quality of life and daily functioning variables that had only a single postbaseline measurement at study end (Q-LES-Q, Sheehan Disability Scale), and as additional secondary analyses for the other

efficacy outcome variables (to evaluate sensitivity of results to choice of statistical method), mean change from baseline to end of study was compared for the sertraline and placebo groups using an analysis of covariance with treatment status as the primary independent variable and clinical site as covariate (using general linear model: PROC GLM in SAS; SAS Institute Inc., Cary, N.C.). For these analyses, the last-observation-carried-forward (LOCF) strategy was used to impute missing end-of-study values based on the last observed data for dropouts. The Cochran-Mantel-Haenszel $\chi^2$ (SAS PROC FREQ; SAS Institute Inc., Cary, N.C.), using the row mean scores test with clinical site as strata, was used to compare categorical outcomes (response proportions). In additional secondary analyses for categorical outcomes, the consistency of treatment effect across clinical sites was assessed using a logistic regression approach with treatment, clinical site, and treatment-by-site interaction terms in the model.

## RESULTS

### Patient Characteristics

Three hundred thirty-eight subjects were randomly assigned to sertraline or placebo treatment groups. Of those, 328 subjects were included in the safety analysis. Ten subjects did not receive at least 1 study medication dose and, hence, were not included in safety and ITT samples. Three hundred twenty-six subjects, of whom 164 received sertraline and 162 received placebo, took at least 1 dose of study medication and had at least 1 postbaseline efficacy assessment, thus constituting the ITT sample.

Two hundred forty-one subjects (74%) completed the study, with 117 subjects (71.3%) in the sertraline group and 124 (76.5%) in the placebo treatment group ($\chi^2 = 1.14$, df = 1, p = .3). The patient progression and reasons for dropout are presented in Figure 1. Study completers did not differ significantly from dropouts with respect to baseline demographic and clinical characteristics. There were no statistically significant differences in reasons for dropping out between the sertraline and placebo groups ($\chi^2 = 4.3$, df = 4, p = .4).

Demographic and clinical characteristics of study subjects are shown in Table 1. No significant differences between the 2 groups in any of the baseline clinical and demographic variables were detected. Women constituted the majority of the study sample, and 8.3% were over the age of 60 years. Over half of study subjects received prior psychotropic treatment (53.7% and 51.2% for the sertraline and placebo groups, respectively), and approximately one fourth had prior psychiatric history (23.2% and 27.7% for the sertraline and placebo groups, respectively). Seventeen percent of the total sample reported previous history of depression, and 3% reported prior history of alcohol abuse.

**Table 1. Demographic and Clinical Characteristics of the Intention-to-Treat Sample at Baseline (N = 326)**

| Characteristic | Treatment Group: Placebo (N = 162) | Treatment Group: Sertraline (N = 164) | Test Statistic (df) | p Value |
|---|---|---|---|---|
| Gender, N (%) | | | 0.4 (1) | .521[a] |
| Female | 92 (56.8) | 98 (59.8) | | |
| Male | 70 (43.2) | 66 (40.2) | | |
| Race, N (%) | | | 0.3 (5) | .577[a] |
| White | 122 (75.3) | 125 (76.2) | | |
| African American | 22 (13.6) | 22 (13.4) | | |
| Other | 18 (11.1) | 17 (10.4) | | |
| Age, mean (SD), y | 40.8 (12.3) | 40.1 (13.2) | 0.5 (1,316) | .488[b] |
| Age at onset, mean (SD), y | 30.2 (8.5) | 29.0 (14.0) | 1.7 (1,315) | .339[b] |
| CGI-S score, mean (SD) | 4.3 (0.5) | 4.4 (0.5) | 1.9 (1,316) | .173[b] |
| MADRS score, mean (SD) | 12.5 (2.7) | 12.7 (2.8) | 1.1 (1,316) | .303[b] |
| HAM-A total score, mean (SD) | 24.1 (2.8) | 24.5 (3.1) | 2.4 (1,316) | .123[b] |

[a]From Cochran-Mantel-Haenszel $\chi^2$ with clinical site as stratification variable.
[b]From analysis of covariance model containing treatment and clinical site as independent variables.
Abbreviations: CGI-S = Clinical Global Impressions of Severity scale, HAM-A = Hamilton Rating Scale for Anxiety, MADRS = Montgomery-Asberg Depression Rating Scale.

### Efficacy

Table 2 provides a summary of study results for efficacy variables for the ITT sample, and Table 3 displays the mean change scores by visit for the 2 main anxiety measures, the HAM-A total score and the patient-rated HADS-anxiety subscale. The downward linear trend in HAM-A total scores over time was significantly different for sertraline versus placebo group (F = 4.66, df = 1,295; p = .032). Estimates of the least squares mean (± SE) end-of-study change in the HAM-A total score (week 10 minus baseline) obtained from the longitudinal analysis were 14.1 (± 0.6) for sertraline and –12.3 (± 0.6) for placebo (LS mean treatment effect [sertraline vs. placebo]: –1.8 ± 0.8; 95% CI = –3.4 to –0.2). The improvement in HAM-A total score for the sertraline group was significantly better than for the placebo group, beginning marginally at week 4 (LS mean treatment effect = –1.0 ± 0.5, t = –1.93, df = 296, p = .055), becoming fully significant at week 6 (LS mean treatment effect = –1.3 ± 0.6, t = –2.12, df = 297, p = .035), and lasting through the end of study week 10 (Table 3).

Significant differences in linear downward trends for sertraline versus placebo were also observed for all secondary efficacy outcome variables except the HAM-A somatic subscale, the CGI-S, and the MADRS (Table 2). Although the linear downward trends in the CGI-S score were not significantly different for sertraline versus placebo, closer examination of the visit-wise comparisons for LS mean change scores indicated a significantly superior improvement for sertraline beginning at week 2 (LS

**Table 2. Efficacy of Sertraline vs. Placebo in Outpatients With Generalized Anxiety Disorder: Change From Baseline to Endpoint for the Intention-to-Treat Sample (N = 326)[a]**

| | Change From Baseline[b] | | Repeated-Measures Analyses[c] | | | | |
|---|---|---|---|---|---|---|---|
| | | | Least Squares Treatment Effect[c] | | Treatment × Time Interaction | | |
| Outcome Variable | Placebo Mean (SE) | Sertraline Mean (SE) | Mean (SE) | 95% CI | F | df | p |
| HAM-A | | | | | | | |
| Total | –11.15 (7.32) | –12.71 (7.17) | –1.8 (0.8) | –3.4 to –0.2 | 4.66 | 1,295 | .032 |
| Psychic subscale | –5.86 (4.54) | –7.05 (4.49) | –1.3 (0.5) | –2.8 to –0.2 | 6.56 | 1,296 | .011 |
| Somatic subscale | –5.30 (3.55) | –5.66 (3.55) | –0.5 (0.5) | –1.5 to 0.5 | 1.00 | 1,290 | .319 |
| Anxious mood (item 1) | –1.12 (1.03) | –1.49 (0.96) | –0.5 (0.1) | –0.3 to –0.07 | 8.81 | 1,292 | .003 |
| Tension (item 2) | –1.14 (1.00) | –1.44 (1.06) | –0.4 (0.1) | –0.2 to –0.6 | 7.22 | 1,291 | .008 |
| HADS | | | | | | | |
| Total | –6.02 (7.22) | –9.12 (7.77) | –3.5 (0.9) | –5.3 to –1.7 | 15.69 | 1,296 | < .001 |
| Anxiety subscale | –4.15 (4.36) | –5.80 (4.49) | –2.0 (0.5) | –3.0 to –1.0 | 10.7 | 1,297 | .001 |
| Depression subscale | –1.87 (3.69) | –3.32 (4.27) | –1.5 (0.4) | –2.4 to –0.6 | 13.9 | 1,289 | < .001 |
| CGI-S | –1.39 (1.28) | –1.67 (1.29) | –0.3 (0.1) | –0.5 to –0.1 | 1.49 | 1,294 | .223 |
| MADRS | –3.49 (5.94) | –4.06 (6.03) | –0.7 (0.7) | –2.01 to 0.7 | 0.62 | 1,256 | .431 |
| Responders, % | | | | | $\chi^2$ | df | p |
| HAM-A ≥ 50% score decrease | 48.2 | 59.2 | | | 3.85 | 1 | .050[d] |
| CGI-I score of 1 or 2 | 54.3 | 64.6 | | | 3.62 | 1 | .057[d] |

[a]Mixed-models analysis.
[b]Raw mean change from baseline to end of study (week 10) using last observation carried forward to impute missing values.
[c]From longitudinal analyses with treatment, week, treatment-by-week, and site as fixed effects (independent variables) and change from baseline as dependent variable. Treatment effect is difference in change from baseline scores for sertraline versus placebo *at week 10* estimated from the model.
[d]p Value from Cochran-Mantel-Haenszel $\chi^2$ with sites as strata.
Abbreviations: CGI-I = Clinical Global Impressions of Improvement scale, CGI-S = Clinical Global Impressions of Severity scale, HADS = Hospital Anxiety and Depression Scale, HAM-A = Hamilton Rating Scale for Anxiety, MADRS = Montgomery-Asberg Depression Rating Scale.

mean treatment effect = –0.1 ± 0.1, t = –2.29, df = 301, p = .023) and continuing through week 8 (LS mean treatment effect = –0.2 ± 0.1, t = –1.95, df = 295, p = .053), with the difference narrowing and becoming nonsignificant at week 10 (LS mean treatment effect = –0.3 ± 0.1, t = –1.85, df = 295, p = .065). The improvement in patient-rated HADS-anxiety subscale scores with sertraline was significant as compared to placebo beginning as early as week 2 (p = .029) and continuing to study end.

The secondary analyses using LOCF to impute missing values for noncompleters corroborated the longitudinal analysis in demonstrating a significant effect of sertraline in reducing levels of anxiety as measured by the mean change from baseline for HAM-A total score (LS mean treatment effect at week 10 [sertraline vs. placebo]: –1.57 ± 0.79, F = 4.01, df = 1,316; p = .047), HAM-A psychic anxiety subscale score (LS mean treatment effect at week 10 = –1.20 ± 0.49, F = 5.9, df = 1,316; p = .015), and HAM-A items 1 (LS mean treatment effect at week 10 = –0.36 ± 0.11, F = 10.9, df = 1,316; p = .001) and 2 (LS mean treatment effect at week 10 = –0.30 ± 0.12, F = 6.7, df = 1,316; p = .010). A significantly greater mean reduction from baseline in the sertraline group was also observed for the HADS total score (LS mean treatment effect at week 10 = –3.19 ± 0.83, F = 14.4, df = 1,311; p < .001), the HADS-anxiety subscale (LS mean treatment effect at week 10 = –1.72 ± 0.49, F = 10.9, df = 1,311; p < .001), and the CGI-S (LS mean treatment effect at week 10 = –0.29 ± 0.14, F = 4.3, df = 1,316; p = .038). The only HAM-A measure of anxiety that did not show significant treatment differences in these secondary analyses was the somatic anxiety subscale.

The proportion of patients who responded to sertraline (based on at least a 50% reduction from baseline in HAM-A total score) was 59.2% compared to 48.2% for placebo ($\chi^2$ = 3.85, df = 1, p = .050). Approximately 64.6% of patients using sertraline achieved a final score at study end of 1 (very much improved) or 2 (improved) on the CGI-I compared to approximately 54.3% of placebo patients ($\chi^2$ = 3.62, df = 1, p = .057). Logistic regression analyses of the dichotomous outcome (responder/nonresponder) found no significant site-by-treatment interaction effect using both response definitions.

Although patients receiving sertraline experienced greater functional improvement as measured by the Sheehan Disability Scale and the Q-LES-Q, neither comparison reached statistical significance (Q-LES-Q [percent score] LS mean treatment effect [sertraline vs. placebo]: 1.26 ± 1.3; F = 0.9, df = 1,313; p = .348) (Sheehan Disability Scale total: –1.28 ± 0.85; F = 2.3, df = 1,252; p = .133).

### Treatment Tolerability

The mean daily dose of sertraline at study endpoint was 149.1 mg (SD = 59.0). Sertraline was generally well tolerated. Thirty-eight subjects (23.5%) discontinued placebo treatment compared with 47 subjects (28.7%) in the sertraline group. The most common reasons for dropout were failure to return (29/85), consent withdrawn

**Table 3. Change From Baseline in Total Scores on the HAM-A and the HADS-Anxiety Subscale During Sertraline vs. Placebo Treatment for Generalized Anxiety Disorder**

| | Change From Baseline Least Squares Mean (SE)[a] | | Longitudinal Analyses[a] | | | |
|---|---|---|---|---|---|---|
| | | | Effect Size | Treatment × Time Interaction | | |
| Efficacy Measure | Placebo | Sertraline | (95% CI)[b] | t | df | p |
| HAM-A | | | | | | |
| Week 1 | –3.63 (0.37) | –3.71 (0.37) | –0.89 to 0.73 | –0.20 | 308 | .843 |
| Week 2 | –5.07 (0.36) | –5.45 (0.36) | –1.16 to 0.41 | –0.94 | 304 | .348 |
| Week 3 | –6.51 (0.38) | –7.18 (0.38) | –1.52 to 0.18 | –1.55 | 298 | .122 |
| Week 4 | –7.96 (0.42) | –8.92 (0.42) | –1.95 to 0.02 | –1.93 | 296 | .055 |
| Week 6 | –9.40 (0.47) | –10.66 (0.48) | –2.42 to –0.09 | –2.12 | 297 | .035 |
| Week 8 | –10.84 (0.54) | –12.39 (0.54) | –2.93 to –0.18 | –2.22 | 298 | .027 |
| Week 10 | –12.29 (0.62) | –14.13 (0.62) | –3.45 to –0.24 | –2.27 | 298 | .024 |
| HADS Anxiety | | | | | | |
| Week 1 | –1.44 (0.27) | –1.83 (0.27) | –0.98 to 0.21 | –1.27 | 306 | .204 |
| Week 2 | –1.94 (0.26) | –2.59 (0.26) | –1.23 to –0.07 | –2.20 | 308 | .029 |
| Week 3 | –2.45 (0.27) | –3.36 (0.27) | –1.52 to –0.30 | –2.95 | 310 | .003 |
| Week 4 | –2.95 (0.29) | –4.13 (0.29) | –1.85 to –0.50 | –3.44 | 311 | < .001 |
| Week 6 | –3.45 (0.32) | –4.89 (0.32) | –2.21 to –0.67 | –3.70 | 309 | < .001 |
| Week 8 | –3.95 (0.35) | –5.66 (0.35) | –2.58 to –0.82 | –3.82 | 307 | < .001 |
| Week 10 | –4.46 (0.40) | –6.42 (0.40) | –2.97 to –0.96 | –3.86 | 304 | < .001 |

[a]The least squares means are estimated from longitudinal analyses with treatment, week, treatment-by-week, and site as fixed effects (independent variables) and change from baseline as the dependent variable.
[b]95% CI on difference in least squares means (sertraline vs placebo).
Abbreviations: HADS = Hospital Anxiety and Depression Scale, HAM-A = Hamilton Rating Scale for Anxiety.

**Table 4. Incidence of Treatment-Emergent Adverse Events Occurring in 10% or More of Subjects or With Significantly Greater Frequency in 1 Treatment Group in the Safety Sample**

| Event | Sertraline, N (%) (N = 165) | Placebo, N (%) (N = 163) | p Value |
|---|---|---|---|
| Diarrhea/loose stools | 29 (17.6) | 19 (11.7) | .129 |
| Insomnia | 28 (17.0) | 24 (14.7) | .578 |
| Nausea | 36 (21.8) | 23 (14.1) | .069 |
| Dry mouth | 23 (13.9) | 14 (8.6) | .126 |
| Libido decreased/loss | 29 (17.6) | 4 (2.4) | < .001 |
| Male Subjects Only | (N = 67) | (N = 71) | |
| Male sexual dysfunction | 12 (17.9) | 0 (0) | < .001 |
| Abnormal orgasm/anorgasmia | 7 (10.4) | | |
| Erectile disturbance | 1 (1.5) | | |
| Ejaculation failure | 4 (6.0) | | |

(19/85), adverse events (12/85), and unsatisfactory response (7/85). No serious adverse events were reported during the study. The most common treatment-emergent adverse events occurring during the study are presented in Table 4. Only sexual side effects (including decrease/loss of libido and male sexual dysfunction) were reported significantly more by subjects receiving sertraline than by subjects receiving placebo.

The values for vital signs, weight, and laboratory tests were generally similar in the sertraline and placebo groups except for an increase in diastolic blood pressure in the sertraline group (mean change = +1.59 mm Hg [SD = 8.83] vs. –0.63 mm Hg [SD = 8.32] in the placebo group, p = .0204) and an increase in weight in the placebo group (mean change = +1.07 lb [SD = 8.56] vs. –1.94 lb [SD = 5.29] in the sertraline group, p = .0002).

## DISCUSSION

This 10-week study shows statistically significant differences in the primary outcome variable—the total HAM-A scores—as well as higher treatment response rates in the sertraline group compared with the placebo-treated group. Improvement was also observed in scores on the HAM-A psychic anxiety subscale, items 1 and 2 of the HAM-A, and the HADS-anxiety subscale. In fact, a considerably stronger signal on the HADS-anxiety subscale, a measure emphasizing psychic rather than somatic anxiety symptoms, was observed. This finding, along with significant improvement in HAM-A psychic subscale scores, suggests that sertraline may preferentially target psychic anxiety symptoms or that psychic anxiety symptoms may be less sensitive to placebo effect—an issue subject to ongoing debate in the literature.[23] Mean changes from baseline were significantly greater for the sertraline-treated group than for the placebo group beginning at week 6 for the HAM-A total score and at week 2 for the patient-rated HADS-anxiety subscale. However, these findings are tempered by the relatively small differences observed between treatment groups and by the fact that scores on the somatic symptom subscale of the HAM-A and measures of functional improvement (Sheehan Disability Scale and the Q-LES-Q) did not differ significantly between the sertraline and placebo groups.

The findings in the current study are generally consistent with results from the first trial of sertraline versus placebo in the treatment of adults with GAD.[12] That 12-week, double-blind, placebo-controlled, flexible-dose

(50–150 mg/day), multicenter, international trial conducted in Australia, Canada, Denmark, Norway, and Sweden reported significantly greater improvement in anxiety symptoms with sertraline than placebo on all outcome variables studied. Comparable response rates were observed for the 2 studies, with 63% of sertraline patients in the international trial[12] and 64.6% of sertraline patients in the current study achieving CGI-I scores of 1 or 2 and 59% of sertraline patients in the international trial[12] compared to 59.2% of sertraline patients in the current trial experiencing at least a 50% decrease from baseline in HAM-A total score. However, as previously mentioned, differences between treatment groups in this trial were smaller than those reported by Allgulander and colleagues.[12] This appears to be primarily due to differences in placebo response rates between the 2 studies. Indeed, the placebo response rates reported here were considerably higher than those reported in the international trial[12] (48.2% vs. 29% and 54.3% vs. 37% for ≥ 50% reduction in total HAM-A scores and for CGI-I scores of 1 and 2, respectively). High placebo response rates in the current study may also account for the lack of statistically significant difference between groups in somatic anxiety symptoms, which were shown to improve significantly with sertraline in the international trial.[23]

High placebo response rates are not unusual in controlled GAD treatment studies,[5,6] and the rates observed in the international trial were particularly low. The reasons for the observed differences in placebo response rates between the 2 sertraline trials may be difficult to pinpoint since both trials were comparable in their overall design and subject demographics, such as gender, duration, and severity of illness. It could be speculated that the lack of placebo lead-in phase prior to randomization in the current study may have contributed to the higher placebo response rates and subsequently lower effect sizes compared with those of the international trial.[23] However, a meta-analysis by Trivedi and Rush,[24] who evaluated 39 efficacy antidepressant trials that used a placebo lead-in and 33 trials that did not, found that the response to placebo during the active phase was nearly identical in both cohorts. Unfortunately, review of the literature revealed no comparable analyses in anxiety disorders treatment trials.

Finally, sertraline treatment was well tolerated. The adverse events profile is similar to previously reported sertraline studies of patients with other anxiety disorders or depression. Only sexual side effects were reported significantly more frequently by patients receiving sertraline than patients receiving placebo.

In summary, we report here results from 1 of the only 2 multicenter studies conducted to explore the efficacy and safety of sertraline in the treatment of GAD patients. Although there were significant between-groups differences in the main outcome measures in both studies, clinicians should be aware that the magnitude of treatment effect reported by Allgulander and colleagues[12] may not always be attained in a given patient population. Given the upcoming availability of the generic form of sertraline on the market, we offer this report to provide clinicians with the most complete available information on sertraline in GAD to aid in the treatment decision-making process in this important group of patients.

*Drug names:* escitalopram (Lexapro), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft), venlafaxine (Effexor).

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