Selective Serotonin Reuptake Inhibitor Treatment for Generalized Anxiety Disorder: A Double-Blind, Prospective Comparison Between Paroxetine and Sertraline

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Objective: Selective serotonin reuptake inhibitors (SSRIs) appear to be an effective class of medications for the treatment of generalized anxiety disorder. Within the SSRI class, however, there have been no comparative treatment studies for this disorder. Therefore, in the present study, we compared the efficacy and tolerability of 2 SSRIs, paroxetine and sertraline, in the treatment of generalized anxiety disorder.

Method: In this parallel-group, double-blind, flexible-dose study, 55 patients with primary generalized anxiety disorder (DSM-IV criteria) were randomly assigned to receive either paroxetine or sertraline treatment for 8 weeks. Primary efficacy measures were the mean changes in Hamilton Rating Scale for Anxiety (HAM-A) scores as well as responder and remission rates based on the Clinical Global Impressions scale. Secondary efficacy measures consisted of the Indiana University Generalized Anxiety Measurement Scale and self-report ratings of anxiety, and quality-of-life outcome. Tolerability was assessed using the Systematic Assessment for Treatment Emergent Events questionnaire for treatment-emergent symptoms.

Results: The intent-to-treat sample consisted of 53 patients who received medication for at least 1 week. Of the 53 patients, 43 completed the entire 8 weeks of treatment. Both paroxetine and sertraline resulted in significant decreases in mean HAM-A scores (paroxetine = 57% ± 28%; sertraline = 56% ± 28%). There were no differences between medication groups on response or remission rates, and tolerability was comparable.

Conclusions: Both paroxetine and sertraline appear similarly effective and well tolerated for the treatment of generalized anxiety disorder.

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Generalized anxiety disorder (GAD) is a chronic anxiety disorder characterized by uncontrollable worry resulting in a number of psychic and somatic symptoms. In recent years, several pharmacologic agents have been developed for the treatment of this illness.[1] In particular, the selective serotonin reuptake inhibitors (SSRIs) are considered one of the first pharmacologic treatment choices. For example, a double-blind, placebo-controlled trial of paroxetine demonstrated efficacy in GAD following 8 weeks of treatment.[2] In a long-term treatment study, subjects were initially treated for 8 weeks with paroxetine, and responders were then randomly assigned to either continued paroxetine or placebo for an additional 6 months. Those subjects who continued to receive paroxetine demonstrated greater maintenance in their treatment response and less risk of relapse.[3]

Although these studies with paroxetine have helped to establish its treatment efficacy for GAD, few studies have compared paroxetine with other SSRI agents for the treatment of GAD. Another SSRI of interest is sertraline, which has been demonstrated to be effective in the treatment of GAD in children and adolescents.[4] Although one could infer the possibility that both paroxetine and sertraline are equally effective treatments for GAD in adults, there have been no empirical studies to test this assumption. Additionally, both agents may be effective, but they may differ in their adverse events associated with treatment, warranting a direct comparison.

The purpose of the present study was to test the hypothesis that paroxetine and sertraline are similar in their effectiveness and tolerability for the treatment of adult GAD. A secondary goal of the study was to examine the effects of these treatments on quality-of-life outcome associated with GAD.

METHOD

Subject Selection

The study was conducted at the Indiana University Anxiety Disorders Clinic, Indianapolis. Subjects were recruited from a variety of sources, including clinic and

physician referrals and direct media advertisement. To be included in the study, subjects had to meet the following criteria: age of 18 years or older, primary DSM-IV[5] diagnosis of GAD, and Hamilton Rating Scale for Anxiety (HAM-A)[6] symptom score of 18 or greater. Subjects were allowed to have other Axis I anxiety and depressive disorders as long as GAD was determined to be the primary illness in a structured interview by the screener as well as a clinical interview with the principal investigator (A.W.G.). Patients were required to be in good physical health as determined by medical history and normal physical examination, electrocardiogram, and laboratory study (renal and liver function tests, thyroid function tests, and complete blood count) results.

Exclusion criteria included having a Hamilton Rating Scale for Depression (HAM-D)[7] score greater than 20 at baseline, a history of substance abuse/dependence within 6 months prior to baseline, a history of psychotic or bipolar disorders, prior nonresponse to an adequate trial of either sertraline or paroxetine, and pregnancy or any other medical conditions that would contradict treatment with either paroxetine or sertraline. Subjects were free from all psychotropic medications prior to randomization for at least 2 weeks, with the exception of those who were taking fluoxetine, which required a 4-week clearance period. Subjects had a negative urine toxicology screen prior to randomization.

Written informed consent was obtained from each subject prior to any study procedures. All study procedures were reviewed and approved by the Indiana University-Purdue University Institutional Review Board.

Study Procedures

Subjects were administered a semistructured clinical interview, the Mini International Neuropsychiatric Interview for DSM-IV,[8] to determine diagnostic eligibility. They were interviewed by a mental health professional who was trained in the use of the instrument as well as in the assessment of anxiety disorders. Following diagnostic eligibility, subjects' primary diagnoses were confirmed by the principal psychiatrist (A.W.G.), and they underwent medical and symptom severity screening. Subjects who met study criteria were then randomly assigned in a double-blind manner to receive either paroxetine or sertraline for 8 weeks. Medications were encapsulated to achieve blinding. Dosages were established in blinded levels from level 1 to level 4. For paroxetine, the initial daily dose level was 10 mg, which was increased to 40 mg at level 4. For sertraline, the initial dose level was 25 mg, which was increased to a maximum of 100 mg at level 4. Subjects were increased flexibly on their dose level during the first 4 weeks of the treatment, after which they were maintained on a fixed dose level. Subjects had to be receiving a minimum dose level of 2 to remain in the study. Medication adherence/compliance was assessed by clinical interview and review of medication bottle returns. Concomitant medication for sleep disturbance was not allowed during the study. Subjects came to the anxiety clinic for weekly study visits during the 8 weeks of the clinical trial.

Efficacy and Tolerability Measures

Efficacy and tolerability of the treatments were assessed at every visit following baseline. The primary efficacy measures consisted of the HAM-A as well as the Clinical Global Impressions-Severity of Illness scale (CGI-S).[9] Treatment response was defined as at least 50% reduction in HAM-A rating scores at endpoint from baseline. Treatment remission was defined as a CGI-S score of 1, i.e., "normal," at treatment endpoint. A secondary remission measure used was a HAM-A score of < 7.

A secondary efficacy measure was the Indiana University Generalized Anxiety Measurement Scale (IU-GAMS),[10] which is a 14-item scale that assesses the core DSM-IV symptoms and features of generalized anxiety: worry amount (mean hours per day), worry severity, worry content (ruminative vs. anticipatory), worry type (realistic vs. catastrophic), difficulty with controlling worry, restlessness, muscle tension, fatigue, difficulty with concentration, irritability, sleep disturbance, gastrointestinal disturbance, inability to relax, and observable behavior within interview. For each item, the clinician rates the symptom on a 1-to-4 scale. Unlike the HAM-A, the IU-GAMS symptoms are anchored at each point to indicate a descriptor for the rating. For example, the item for concentration is rated 1—nearly always able to concentrate; 2—generally able to concentrate, some difficulties with complex tasks; 3—occasionally able to concentrate, must focus with effort; or 4—almost never able to concentrate, routine tasks affected. The IU-GAMS has demonstrated good item reliability, interrater reliability, and convergent validity with the HAM-A.[10]

Besides the clinician-rated scales, efficacy was also assessed using the self-report questionnaire of the Beck Anxiety Inventory (BAI).[11] Quality of life was examined using the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[12] which assesses satisfaction with different health, work, and social domains. In addition, at each weekly visit, subjects were questioned regarding any adverse effects. Tolerability was assessed by changes in the ratings on the Systematic Assessment for Treatment Emergent Events (SAFTEE)[13] questionnaire from baseline to endpoint. The SAFTEE consists of a number of symptoms that may occur in association with either illness or treatment, and these symptoms are rated from 0—"not present" and 1—"mild" to 3—"severe" by the clinician following an interview with the patient.

Statistical Methods

The analyses for efficacy were conducted on the intent-to-treat (ITT) group, which was defined as subjects who

Table 1. Demographic and Clinical Characteristics for ITT Sample of Patients With Generalized Anxiety Disorder

Characteristic	Paroxetine (N = 25)	Sertraline (N = 28)
Female, %	84	71
Age, mean ± SD, y	35.6 ± 11.7	42.9 ± 14.7
Ethnicity, %		
White	84	93
Black	12	7
Asian	4	
Education, mean ± SD, y	15.3 ± 2.5	15.4 ± 2.8
Comorbidity, %		
None	60	64
Social anxiety	8	4
Panic	0	4
Depression/dysthymia	32	28
Baseline scores, mean ± SD		
HAM-A	20.8 ± 2.3	21.4 ± 3.4
IU-GAMS	33.6 ± 4.2	35.3 ± 5.6
CGI-S	4.2 ± 0.41	4.4 ± 0.56
BAI	10.9 ± 4.4	12.3 ± 9.5
Q-LES-Q	62 ± 10	64 ± 16

Abbreviations: BAI = Beck Anxiety Inventory, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, ITT = intent-to-treat, IU-GAMS = Indiana University Generalized Anxiety Measurement Scale, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

had received at least 1 dose of medication and had returned for at least 1 postbaseline assessment. The last-observation-carried-forward method was used for imputations of missing data. Repeated-measures analyses of variance (ANOVAs) were conducted to examine treatment differences over time for the primary and secondary outcome variables. The between-subject variable was group assignment. Repeated-measures ANOVAs were also conducted with comorbidity as a between-subject variable to determine any effects of comorbid diagnosis on the outcome variables. All statistical tests were 2-sided and assumed a .05 level of significance.

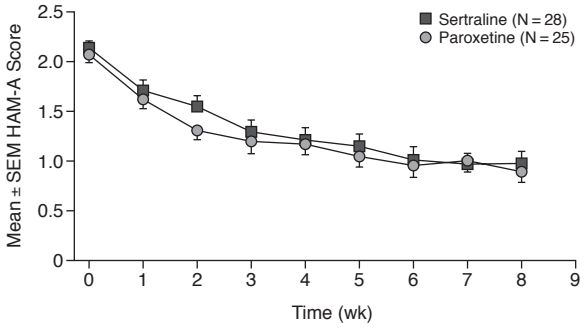
The initial power estimates were based on the hypothesis that the proportion of response to sertraline would not be significantly inferior to the proportion of response as previously established by paroxetine. Using 65% as the response rate for the established treatment (paroxetine), a sample size of 32 for the paroxetine group and 32 for the sertraline group would establish a 65% power at a .10 significance level using a 1-sided equivalence test of proportions. The hypothesis was that the rate in the paroxetine group would be 0.65 and that the response rate for the sertraline group would be no worse than the 65% rate, with a maximum allowable difference of 20% for the range of equivalence.[14]

RESULTS

Patient Characteristics

Sixty-one subjects underwent baseline evaluation. Of these 61 subjects, 6 who were screened failed study entry for medical or diagnostic reasons. Therefore, 55 subjects were randomly assigned to treatment, but 2 did not return postbaseline, leaving an ITT sample of 53 subjects. Patient demographics and clinical characteristics for this sample are presented in Table 1. The 2 medication groups did not differ significantly in ethnicity, years of education, or comorbidity of diagnosis; those within the sertraline group tended to be older (t = 1.92, df = 51, p = .06). They also did not differ on their baseline clinical symptom severity or quality-of-life scores.

Figure 1. Hamilton Rating Scale for Anxiety (HAM-A) Total Score for ITT Sample of Patients With Generalized Anxiety Disorder



Abbreviation: ITT = intent-to-treat.

The number of subjects who completed the entire 8 weeks of treatment was 43 (78%). The 2 medication groups did not differ in the percentage of subjects who withdrew early (paroxetine, 20% [5/25]; sertraline, 18% [5/28]; $\chi^2 = 0.04$, df = 1, NS) nor in the reasons for withdrawal ($\chi^2 = 4.6$, df = 4, NS). Of the 10 subjects who withdrew early, 1 withdrew due to lack of efficacy, 6 withdrew due to adverse events, and 3 withdrew due to other factors, such as moving or time conflicts. The primary adverse events for the paroxetine group were dizziness, nausea, sexual dysfunction, and constipation, whereas the primary adverse events for the sertraline group were sexual dysfunction and diarrhea.

Mean ± SD dosage level for the paroxetine group was 2.84 ± 0.89 (e.g., 28.4 ± 8.9 mg/day), whereas the mean dosage level for the sertraline group was 3.14 ± 0.89 (e.g., 78.5 ± 22.5 mg/day). The median dose level for both groups was 3.0, i.e., 30 mg of paroxetine and 75 mg of sertraline.

Efficacy Results

Primary outcome measures. Figure 1 shows reductions in HAM-A scores. Both the sertraline and paroxetine groups experienced significant reductions from baseline to end of treatment (F = 207, df = 1,51; p < .001); however, there was no significant group effect (F = 0.37, df = 1,51; NS). The mean percent reduction in HAM-A scores

Table 2. Percentage of Change in Secondary Outcome Measure Scores for ITT Sample of Patients With Generalized Anxiety Disorder, Mean ± SD[a]

Measure	Paroxetine (N = 25)	Sertraline (N = 28)
IU-GAMS	40 ± 16	36 ± 20
BAI	64 ± 42	59 ± 43
Q-LES-Q	25 ± 19	24 ± 30

[a]All percentages reported in direction of improvement.
Abbreviations: BAI = Beck Anxiety Inventory, ITT = intent-to-treat, IU-GAMS = Indiana University Generalized Anxiety Measurement Scale, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

was 57.3% ± 27.6% for the paroxetine group and 55.9% ± 27.6% for the sertraline group. With treatment response defined as at least 50% reduction in score from baseline to posttreatment, the percentage of treatment responders was 68% (17/25) in the paroxetine group and 61% (17/28) in the sertraline group ($\chi^2 = 0.3$, df = 1, NS). The percentage of subjects with posttreatment HAM-A scores of less than 7 was 40% (10/25) within the paroxetine group and 50% (14/28) within the sertraline group.

Remission rates were defined as a CGI-S score of 1, normal, at posttreatment. The remission rate for the paroxetine group was 40% (10/25), whereas remission was achieved by 46% (13/28) of the sertraline group ($\chi^2 = 0.22$, df = 1, NS). Analyses based solely on those who completed the entire 8-week trial supported no differences between the 2 groups on either HAM-A ratings (F = 0.42, df = 1,37; NS) or posttreatment CGI-S ratings (F = 1.16, df = 1,37; NS). Mean reduction in HAM-A scores for the ITT sample did not differ by the presence of a comorbid condition (F = 0.01, df = 1,49; NS), nor was there an interaction between comorbidity and medication group (F = 1.5, df = 1,49; NS). Overall, both groups demonstrated a greater reduction on the HAM-A psychic subscale (mean decrease = 61% ± 28%) than on the somatic subscale (mean decrease = 47% ± 44%) (F = 6.7, df = 1,51; p = .012), with no difference between medication groups (F = 0.01, df = 1,51; NS).

Secondary outcome measures. Table 2 displays the outcomes for the reductions in IU-GAMS scores and self-report BAI scores. The groups demonstrated significant improvement across treatment (F = 168, df = 1,51; p < .001) for the IU-GAMS scores, but there was no significant group effect (F = 1.36, df = 1,51; NS). With treatment response defined as a reduction greater than 50% in IU-GAMS scores from baseline to posttreatment, 40% (10/25) of the paroxetine group responded compared with 25% (7/28) of the sertraline group ($\chi^2 = 0.77$, df = 1, NS). Unlike with the HAM-A scores, both groups demonstrated similar reduction on the IU-GAMS psychic items (mean decrease = 38% ± 21%) and on the somatic items (mean decrease = 39% ± 19%) (F = 0.01, df = 1,51; NS), with no difference between medication groups (F = 0.79, df = 1,51; NS).

Percent reductions in BAI scores also did not differ between groups (F = 0.23, df = 1,50; NS). Quality-of-life scores improved with treatment (F = 40.7, df = 1,46; p < .001), but did not significantly differ between medication groups (F = 0.08, df = 1,46; NS). Only 30.2% (16/53) of subjects scored within community norms on the Q-LES-Q at baseline; after treatment, 73.6% (39/53) were within community norms of a score greater than 70. Analyses based only on completers also demonstrated no difference between groups on the IU-GAMS scores (F = 1.62, df = 1,37; NS), BAI scores (F = 2.07, df = 1,35; NS), or Q-LES-Q scores (F = 0.08, df = 1,35; NS). Mean reduction in IU-GAMS scores for the ITT sample did not differ by the presence of a comorbid condition (F = 0.55, df = 1,49; NS), nor was there a significant interaction between comorbidity and medication group (F = 2.4, df = 1,49; NS).

Symptoms associated with both illness and treatment effects were assessed by the SAFTEE scores, which were compared from the initial visit throughout treatment. The mean baseline SAFTEE score was 19.11 ± 7.83 for the paroxetine group and 17.96 ± 5.79 for the sertraline group. Groups did not differ on their SAFTEE scores at posttreatment (F = 0.10, df = 1,49; NS), although scores did decrease overall with treatment (F = 106, df = 1,49; p < .001). The mean percentage decrease was 57% ± 40% for the paroxetine group and 59% ± 31% for the sertraline group.

DISCUSSION

The findings of the present study demonstrate that both sertraline and paroxetine appear similar in their efficacy in the short-term treatment of GAD. After 8 weeks of treatment, both groups demonstrated significant reductions on the primary and secondary efficacy measures. Our 68% response rate for paroxetine, based on the HAM-A scores, was similar to the 70% response rate found in the placebo-controlled trial of paroxetine.[2] Similarly, Stocchi et al.[3] showed a remission rate of 42% after 8 weeks of treatment. In our study, the remission rate within the paroxetine group was 40% based on either the HAM-A scores or the CGI-S scores. Therefore, the robustness of these results indicates that paroxetine and sertraline can effectively treat the severity of generalized anxiety symptoms and that a substantial proportion of subjects can achieve remission in a relatively short time frame. Our efficacy results also nicely parallel recent work that demonstrated similar efficacy between sertraline and paroxetine for the treatment of panic disorder.[15]

Although sertraline and paroxetine were effective for overall symptom reduction, the results also showed that, as measured by the HAM-A, the SSRI treatments were more effective in reducing the psychic symptoms than the somatic symptoms associated with GAD. Following

treatment, the psychic subscale showed a greater mean percent reduction in symptoms compared with the somatic scale. Other studies, such as the study by Pollack et al.,[2] have also found differences in SSRI effectiveness between the psychic and somatic HAM-A subscales. In our study, however, when we used the IU-GAMS as the efficacy measure, we found equivalent reduction in both the psychic and somatic symptoms. Whereas the HAM-A somatic subscale comprises a number of ubiquitous physical symptoms, the IU-GAMS somatic symptoms consist of those core symptoms specifically associated with GAD, such as restlessness, muscle tension, and irritability. Therefore, the difference between psychic and somatic symptom reductions is likely to be a function of the measurement tool rather than selective effectiveness of the 2 drugs.

One of the strengths of this study is that patients were chosen for having a primary GAD diagnosis, but comorbidity was allowed for inclusion into the study. This entry criterion allows a more naturalistic comparison and a greater generalizability of the present results to a clinical population, given that the majority of patients with GAD clinically present with a secondary anxiety or affective illness.[16] The presence of a comorbid condition did not alter the treatment efficacy of either paroxetine or sertraline.

Another strength of the study is that flexible dosage was allowed so that treatment efficacy could be maximized for the individual subject. The maximum daily dose decision was based on the previous trial, in which the mean effective dose for paroxetine was 26.8 ± 7.5 mg[2]; thus, 40 mg was considered sufficient for the paroxetine group; the 100-mg dose level for sertraline was established due to the findings that paroxetine is approximately twice as potent a serotonergic reuptake inhibitor compared with sertraline.[17] Patients were given initial dose levels that were increased depending on efficacy and tolerability. In a double-blind, placebo-controlled, fixed-dose comparison study, both 20 mg and 40 mg of paroxetine were more effective than placebo for the treatment of GAD, and the 40-mg dose did not appear to be superior.[18] However, in our study, the median daily dose for paroxetine was 30 mg, indicating that dosage greater than 20 mg may be necessary for a significant portion of the subjects. For those who received sertraline, the median dose was 75 mg per day.

Overall, the medications were well tolerated for both groups. The early withdrawal rate of subjects due to adverse symptoms was 11%, which is comparable to previous clinical trials with paroxetine and sertraline (e.g., Rickels et al.[18] and Liebowitz et al.[19]). The assessment of symptoms on a weekly basis using the SAFTEE showed a similar pattern in the emergence and reduction of symptoms across the treatment period for both groups, suggesting that neither group had a greater proportion of adverse symptoms. In addition to reducing symptom severity, both paroxetine and sertraline were associated with improvements in life satisfaction. On the Q-LES-Q, both treatment groups improved in their reported satisfaction and functioning within different life areas. Of particular interest was that 54% of the subjects increased their satisfaction from levels below community norms to within community norms so that by the end of treatment, approximately 74% of the entire sample was within a normal range of satisfaction with various life domains.

In considering the effectiveness of these medications, one limitation of this study is that we did not include a placebo group nor did we try to eliminate possible placebo responders. Although placebo response is always a consideration in clinical trials, the response rate for those subjects treated with paroxetine in this study appeared comparable to the response rate of subjects treated with paroxetine in other studies that utilized placebo controls and found greater efficacy for the active medication. Another consideration is that we based compliance on patient report and pill counts, but did not obtain actual blood drug levels. Surreptitious benzodiazepine use did not appear to be a problem in the present study, as evidenced by negative pretreatment and posttreatment urine benzodiazepine screens. An additional concern could be the sample sizes of each group and whether a larger sample would have found statistically significant differences between groups. Our final study sample was somewhat smaller than the initial target of 32 per group.

In summary, the results of the present study provide useful guidelines for the physician treating the patient with GAD. Both paroxetine and sertraline serve as effective treatments that not only reduce the severity of anxiety, but also enhance life satisfaction. Given the broader inclusion criteria of this study compared with other clinical trials, physicians can be assured that our efficacy results will generalize to their clinical patients.

Drug names: fluoxetine (Prozac and others), paroxetine (Paxil and others), sertraline (Zoloft).

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