A Double-Blind, Placebo-Controlled Study Comparing the Effects of Sertraline Versus Amitriptyline in the Treatment of Major Depression

R. Bruce Lydiard, Ph.D., M.D., Stephen M. Stahl, M.D., Ph.D., Marc Hertzman, M.D., and Wilma M. Harrison, M.D.

Background: This study was designed to compare the efficacy, safety, tolerability profiles, and effects on quality of life of the serotonin selective reuptake inhibitor antidepressant sertraline versus the nonselective tricyclic antidepressant amitriptyline and placebo in patients with major depression.

Method: Outpatients with DSM-III-R major depression were randomly assigned to double-blind treatment for 8 weeks with sertraline (50–200 mg daily), amitriptyline (50–150 mg daily), or matching placebo. Assessments included the Hamilton Rating Scale for Depression, Montgomery-Asberg Depression Rating Scale, Clinical Global Impressions-Severity of Illness scale, Clinical Global Impressions-Improvement scale, Global Assessment Scale, Profile of Mood States, Beck Depression Inventory, Quality of Life Enjoyment and Satisfaction Questionnaire, and Health-Related Quality of Life battery.

Results: All treatment groups demonstrated statistically significant improvement from baseline in depression ratings by Week 1 and thereafter. The antidepressant effects of amitriptyline and sertraline were significantly ($p < .05$) greater than placebo and did not differ significantly from each other. Sertraline was associated with significantly ($p < .05$) greater subjective (i.e., patient-rated) improvement in mood than amitriptyline or placebo. Both active drugs were associated with greater improvements than placebo on most quality of life measurements. On several items, sertraline, but not amitriptyline, was superior to placebo. There was a discernible effect of sertraline earlier than amitriptyline on most quality of life scales. Amitriptyline therapy was associated with significantly more treatment-related adverse events, and discontinuations due to treatment-related adverse events, in comparison to both sertraline and placebo therapy.

Conclusion: Sertraline and amitriptyline each were effective treatments for major depression as assessed by both physician- and patient-rated scales. These results show that sertraline therapy is better tolerated than amitriptyline therapy. Quality of life was also improved by effective antidepressant treatment, with sertraline showing a tendency to produce greater improvements on quality of life measures.

(J Clin Psychiatry 1997;58:484–491)

Received Jan. 9, 1996; accepted Aug. 7, 1997. *From the Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston (Dr. Lydiard), the Clinical Neuroscience Research Center in San Diego and the Department of Psychiatry, University of California San Diego (Dr. Stahl), George Washington University Medical Center, Washington, D.C. (Dr. Hertzman), and Pfizer, Inc., New York, N.Y. (Dr. Harrison).*

This study was supported by Pfizer Inc.

The following investigators also participated in this multicenter clinical trial: Lynn Cunningham, M.D., Bharat Raj Nakra, M.D., John Feighner, M.D., Cecilia Peabody, M.D., James Ferguson, M.D., Robert Riesenberg, M.D., Jon Heiser, M.D., Charles Weise, M.D., and Jeffrey Mattes, M.D.

Reprint requests to: R. Bruce Lydiard, Ph.D., M.D., Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, 171 Ashley Avenue, Charleston, SC 29425.

Major depression is a common psychiatric disorder with high morbidity, mortality, psychosocial, and financial costs.[1,2] Effective antidepressants of the heterocyclic and monoamine oxidase inhibitor classes have been available for many years.[3,4] However, most are associated with unpleasant side effects,[5] toxicity in overdose,[6,7] or unacceptable dietary restrictions that may limit their acceptability to patients.[8] Lack of adequate compliance or premature discontinuation of therapy can lead to relapse. Additionally, many patients require long-term maintenance treatment, which may be compromised if treatment is associated with intolerable side effects.[9–11] Many of the serious and unpleasant side effects associated with the older antidepressants are caused by their pharmacologic actions on multiple neurotransmitter receptors that are unrelated to antidepressant action.[8] The serotonin selective reuptake inhibitor (SSRI) antidepressants have selective neurotransmitter receptor effects, more acceptable side effect profiles than the older antidepressants, and improved safety, with equal efficacy.[12]

However, few studies have investigated whether these assumptions about new serotonin selective antidepressants are accurate, especially from the patient's perspective.[13] If antidepressant treatment does not offer an improved overall quality of life, it is unlikely that a patient will continue taking the medication at optimal therapeutic doses for a sufficient length of time. Quality of life evaluations assess, from the viewpoint of the patient, the global impact of elements related to tolerability and side effect

profile as well as the efficacy of an antidepressant. The investigation of quality of life issues allows for a different perspective from the more limited physician-assessed depression rating scales commonly used as primary outcome variables in clinical studies.[14–16] In addition to the standard assessments of efficacy, tolerability, and safety, this clinical study was designed specifically to compare and contrast the effects on quality of life of the SSRI sertraline, the conventional tricyclic amitriptyline, and placebo in the treatment of outpatients with DSM-III-R major depression.

Amitriptyline was selected as the comparator in this study because it was the most frequently prescribed tricyclic antidepressant (TCA) in the United States at the time this study was designed[17] and is currently the third most frequently prescribed antidepressant. Since most antidepressants are prescribed by non-psychiatrists, the use of amitriptyline may reflect the prescribing patterns of the larger (e.g., non-psychiatrist) pool of prescribers more closely than prescriptions by mental health specialists. TCAs such as amitriptyline exhibit efficacy equal to the newer agents and are available as inexpensive generic formulations. Using the "equal efficacy/lower cost" rationale, managed health care formulary guidelines often encourage clinicians to prescribe generic TCAs before approving the use of newer agents. Thus, using this widely prescribed agent as a comparator seems appropriate for this quality of life study.

METHOD

Study Design

Fifteen U.S. sites participated in this study. Institutional Review Board (IRB) approval of the study protocol was obtained before initiation of the study. Written informed consent was provided by all study patients after the study and its possible outcomes were fully explained to them. The study employed a prospective, double-blind, three-armed, parallel-group, placebo-controlled design with an 8-week active drug treatment period after a 1-week, single-blind, placebo washout period. Patients were selected on the basis of inclusion and exclusion criteria after a clinical interview, medical history, physical examination, electrocardiograph (ECG), and laboratory tests. Patients were withdrawn from all prior psychoactive medication (except for intermittent use of chloral hydrate or temazepam as a hypnotic) and treated with single-blind placebo for 1 week to ensure that no interaction between active study drugs and previous psychotropics occurred and to identify any participants who were rapid placebo responders (i.e., those whose depression improved substantially while receiving placebo). At the end of the washout (baseline), those patients fulfilling the entrance criteria were randomly assigned to double-blind treatment with sertraline, amitriptyline, or placebo for 8 weeks. Assessments of safety, tolerability, and efficacy were performed at baseline and each study visit (Weeks 0, 1, 2, 4, 5, 6, 7, and 8), or at study exit for early discontinuation.

Patient Selection

To be included in the study, patients had to be at least 18 years old, outpatients with a DSM-III-R primary Axis I diagnosis of major depression (single or recurrent), with a duration of the current episode of not less than 4 weeks. They were required to have a 17-item Hamilton Rating Scale for Depression (HAM-D) score greater than or equal to 18, and to have shown no more than slight improvement during placebo washout (a Clinical Global Impressions-Improvement scale [CGI-I] score ≥ 3).

Patients fulfilling DSM-III-R criteria for any of the following conditions were excluded from participation in the study: acute or chronic organic mental disorder, organic brain syndrome, dysthymia, bipolar disorder, severe generalized anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, schizophrenia, paranoid disorders, psychotic disorders not elsewhere classified, or severe personality disorders. In addition, subjects with significant medical illness, a recent history of substance abuse or dependence, current suicide risk, history of neurologic disease, or narrow-angle glaucoma or significant prostate symptoms (such that treatment with amitriptyline would be contraindicated) were excluded from participation. Patients were excluded if they were judged to require additional psychotropic drugs during the study, had previously received sertraline, were within 1 month of participation in an investigational drug study, had failed to respond to adequate trials of two or more antidepressants, had received any depot neuroleptic within 6 months, had received fluoxetine within 1 month, had taken any daily psychotropic medication within 2 weeks, or had received monoamine oxidase uptake inhibitors (MAOIs) within 3 weeks of baseline. Patients with significant laboratory or ECG abnormalities were excluded, and women of childbearing potential were required to be practicing reliable contraception, and to have a negative pregnancy test prior to study entry.

Dosage Regimens

All medication was provided as identical capsules in blister pack format and was administered orally. The study design permitted dose titration. Although titration was intended to be based on patient response in terms of both efficacy and adverse events, there was an inherent tendency to escalate doses, unless limited by adverse events, because the timepoints at which dose adjustments could be made were at short enough intervals that the full therapeutic effect of the previous dose was not likely to be evident. Patients initially received a total daily dose of 50 mg of sertraline, 50 mg of amitriptyline,

or matching placebo. At Week 2, these doses could be increased to 100 mg of sertraline, 100 mg of amitriptyline, or matching placebo; at Week 4, to 150 mg of sertraline, 125 mg of amitriptyline, or matching placebo; and at Week 5, to a maximum of 200 mg of sertraline, 150 mg of amitriptyline, or matching placebo. The dose at Week 5 was to be continued for the rest of the study unless either (1) intolerable side effects occurred, in which case the investigator could decrease the patient's dose by 50 mg of amitriptyline or sertraline; or (2) insufficient improvement occurred, in which case the investigator could increase the dose to a maximum of 200 mg sertraline or 150 mg amitriptyline. At each visit, patients were questioned about compliance, and capsule counts were performed to monitor study drug usage.

Safety Assessments

Physical examination, laboratory tests, and 12-lead ECGs were performed pre- and posttreatment. Nondirective questions about toleration/adverse events were asked at all visits, and all adverse events were recorded whether or not they were considered related to treatment.

Efficacy Assessment

Several outcome measures were chosen a priori to focus on both efficacy and quality of life factors. Physician-assessed parameters included the 17-item HAM-D (at all visits),[18] Clinical Global Impressions-Severity of Illness scale (CGI-S) and CGI-I scores (at all visits),[19] and Global Assessment Scale (GAS)[20] and Montgomery-Asberg Depression Rating Scale (MADRS)[21] (at baseline and all subsequent visits). Patient-assessed measures included the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[22] (at screening, baseline, Weeks 2 and 8, or upon study discontinuation), Health-Related Quality of Life battery, version II (HRQOL-II) (at screening, baseline, Weeks 2 and 8, or upon study discontinuation),[23] Profile of Mood States (POMS)[24] (at baseline and all subsequent visits), and the Beck Depression Inventory (BDI) (at baseline and all subsequent visits).[25] Treatment response was defined using two criteria: achievement of a 50% or greater reduction on HAM-D total score or a CGI-I score ≤ 2 at the final visit.

Statistical Analysis

A .05 alpha level was assumed throughout the analysis in order to declare significance, and two-sided statistical tests were performed using the Statistical Analysis System (SAS) version 6.07 (SAS Institute, Cary, N.C.). The effective sample was the intent-to-treat group of patients (i.e., all patients who took at least one dose of double-blind medication and had a baseline and at least one follow-up assessment). The analyses of continuous variables were performed using the SAS general linear models procedure (PROC GLM), and type III sum of squares hypotheses were tested. Categorical data were analyzed with chi-square and Fisher's exact tests. The groups were assessed for comparability at baseline with respect to demographic characteristics and severity of illness on the basis of primary and secondary efficacy measurements.

The primary measurements of efficacy were the HAM-D 17-item total score and the depression item (Item 1), CGI-S and CGI-I scores, MADRS total score, POMS total score and Factors 2 (depression/dejection) and 4 (vigor), and the improvement in quality of life as assessed by Q-LES-Q and HRQOL-II scales. The between-group effectiveness of treatment was estimated by calculating for each patient the change from baseline to all applicable follow-up assessments of these scales, including the last visit in study (last observation carried forward; LOCF), and evaluating analyses of covariance (ANCOVA) models with respect to treatment group and center main effects and the treatment group × center interaction effects. Significant omnibus F tests were further explored with unpaired t tests. The significance of the within-group changes from the baseline were determined with paired t tests.

Additional analyses were provided by comparing responder rates between treatment groups for the HAM-D and CGI. Overall significance and between-group patterns were determined with chi-square tests.

Safety and toleration of therapy were explored with respect to discontinuation rates, reasons for early study termination, and incidence rates for adverse events regardless of causality, which were summarized by body organ system and World Health Organization (WHO) dictionary-preferred terms. The significance of between-group differences in incidence rates was determined with chi-square tests. The significance of within-group and between-group changes in vital signs and body weight was determined with paired and unpaired t tests, respectively.

RESULTS

Four hundred seventy-three patients entered single-blind washout. Of these, 392 were randomly assigned to double-blind drug treatment. The intent-to-treat population consisted of 385 patients. One hundred twenty-three patients withdrew from the study prematurely; the reasons and proportions for discontinuation are given in Table 1. Discontinuations due to lack of efficacy were highest (9.3%) in the placebo-treated group.

The three study groups were similar with respect to distribution by age, sex, concurrent illnesses, number of previous episodes of major depression, and mean duration of current episode of depression (Table 2). No differences that would affect the validity of the subsequent study analyses and conclusions were found. The patients

Table 1. Number of Patients Completing the Study, Discontinuations, and Reasons for Discontinuation of Double-Blind Therapy

	Sertraline		Amitriptyline		Placebo		Total	
Category	N	%	N	%	N	%	N	%
Patients receiving double-blind therapy	132		131		129		392	
Patients completing study	96	72.7	81	61.8	92	71.3	269	68.6
Patients discontinued	36	27.3	50	38.2	37	28.7	123	31.4
Reasons for discontinuation								
Lost to follow-up	5	3.8	9	6.9	8	6.2	22	5.6
Administrative decision	0	0.0	1	0.8	0	0.0	1	0.3
Insufficient clinical response	9	6.8	5	3.8	12	9.3	26	6.6
Adverse experience	11	8.3	23	17.6	4	3.1	38	9.7
Laboratory or ECG abnormality	2	1.5	1	0.8	2	1.6	5	1.3
Intercurrent illness	0	0.0	4	3.1	3	2.3	7	1.8
Other	9	6.8	7	5.3	8	6.2	24	6.1

were predominantly middle-aged, female, and had recurrent major depression with an index episode of major depression averaging 19 months (median = 10 months).

The mean duration of double-blind therapy was approximately 7 weeks for the intent-to-treat group; however, the mean duration was significantly longer for sertraline (50.1 days, p = .003) and placebo (48.5 days, p = .028) than for amitriptyline (43.2 days).

The mean dose of sertraline at time of initial response (defined as the first assessment period in which patients were rated with a CGI-I score of ≤ 2: very much or much improved) was 90.8 mg and for amitriptyline was 91.3 mg. The modal or most frequently taken doses at time of response were 50 mg/day for sertraline and 100 mg/day for amitriptyline. The mean final dose of study drug was 138.6 mg/day for sertraline and 103.1 mg/day for amitriptyline in the intent-to-treat population. Primary efficacy results are summarized for the intent-to-treat population in Table 3. The mean baseline HAM-D total scores of 21.5 for sertraline, 22.1 for amitriptyline, and 22.1 for placebo indicated that the average participant was moderately depressed. This was supported by analogous baseline mean CGI-I scores. Patient-assessed POMS Factor 2 and POMS Factor 4 scores at baseline indicated that, on average, patients in all treatment groups rated themselves as moderately depressed/dejected and lacking in vigor, which was consistent with the physician ratings. No significant differences were found between treatment groups for baseline HAM-D, MADRS, POMS Factor 4, POMS Factor 2, or CGI-S, indicating that the groups were comparable.

Table 2. Demographic Information*

Demographic Variable	Sertraline	Amitriptyline	Placebo
Number of patients	132	131	129
Sex (% female)	64.4	68.7	66.7
Age (y), mean	41.2	39.0	40.2
Race, N (%)			
White	122 (92.4)	124 (94.7)	123 (95.3)
Black	5 (3.8)	5 (3.8)	3 (2.3)
Asian	1 (0.8)	0 (0.0)	0 (0.0)
Other	4 (3.0)	2 (1.5)	3 (2.3)
Diagnosis, N (%)			
MDD, single	38 (28.8)	39 (29.8)	51 (39.5)
MDD, recurrent	94 (71.2)	92 (70.2)	78 (60.5)
Duration of current MDD episode (mo), mean	17.7	20.1	19.3
Chronic major depression (≥ 24 months), N (%)	68 (51.5)	65 (49.6)	47 (36.4)
Severity of MDD, N (%)			
Mild	6 (4.5)	8 (6.1)	6 (4.7)
Moderate	100 (75.8)	100 (76.3)	102 (79.1)
Severe			
Previous depressive history (y)			
Duration, mean	10.2	9.8	8.5
Range	0–44	0–45	0–46

*Abbreviation: MDD = major depressive disorder.

Clinician Ratings

All three treatment groups demonstrated significant within-group improvement from baseline by Week 1 and thereafter in mean HAM-D Item 1, mean CGI-S, mean CGI-I, and mean MADRS total. For both active drug groups, these changes were significantly superior to those of the placebo group at the last visit (Table 3).

The mean change from baseline in HAM-D Item 1, depression, showed significant improvement for the two active treatment groups over placebo at the last visit. At Week 2, sertraline showed a significant improvement over amitriptyline (p = .038), after which the groups were similar. For mean CGI-S and CGI-I scores, both the sertraline and amitriptyline groups demonstrated comparable improvement that was significantly greater than the improvement of the placebo group at the last visit.

Responders Versus Nonresponders

Fifty-five percent of the sertraline-treated patients were responders, using the criterion of a 50% reduction in baseline HAM-D total score, in comparison to 53% of amitriptyline recipients and 37% of placebo recipients. Response rates for both sertraline and amitriptyline groups were significantly better than for placebo (p = .002 and p = .009, respectively), but no different from each other.

Using the responder criterion of a last visit CGI-I of ≤ 2, it was demonstrated that both active drug groups con-

Table 3. Mean ± SE Changes in Efficacy Variables From Baseline to Last Visit for the Intent-to-Treat Population*

	Sertraline					Amitriptyline					Placebo					Between-Treatment p Values
		Baseline		Change			Baseline		Change			Baseline		Change		
Rating	N	Mean	SE	Mean	SE	N	Mean	SE	Mean	SE	N	Mean	SE	Mean	SE	
Physician ratings																
HAM-D, 17-item total score	119	21.5	0.24	–11.1	0.63[a,b]	104	22.1	0.26	–12.8	0.67[a,b]	115	22.1	0.25	–8.8	0.65[a]	.004
HAM-D, Item 1	130	2.8	0.05	–1.5	0.10[a,b]	129	2.7	0.05	–1.5	0.10[a,b]	126	2.7	0.05	–1.1	0.11[a]	.006
CGI-S	130	4.2	0.04	–1.4	0.11[a,b]	129	4.1	0.04	–1.4	0.11[a,d]	126	4.1	0.04	–0.9	0.11[a]	<.001
CGI-I	130	3.9	0.05	–1.4	0.11[a,b]	129	3.9	0.05	–1.5	0.11[a,c]	126	3.9	0.05	–1.0	0.11[a]	.005
GAS	126	54.2	0.45	16.3	1.23[a,d]	124	53.7	0.46	15.7	1.24[a,b]	122	54.4	0.47	10.0	1.26[a]	<.001
Patient ratings																
BDI	127	14.6	0.56	–7.5	0.59[a,d]	128	15.0	0.56	–6.9	0.60[a,c]	124	14.3	0.57	–4.7	0.61[a]	.003
POMS, Factor 2	128	1.9	0.08	–1.0	0.08[a,d]	127	1.9	0.08	–0.8	0.08[a,b]	125	1.9	0.08	–0.5	0.08[a]	<.001
POMS, Factor 4	128	1.0	0.06	0.6	0.08[a,c]	127	0.9	0.06	0.5	0.08[a,b]	125	1.0	0.06	0.3	0.08[a]	.008

*Abbreviations: BDI = Beck Depression Inventory, CGI-I = Clinical Global Impressions-Improvement Scale, CGI-S = Clinical Global Impressions-Severity of Illness, GAS = Global Assessment Scale, HAM-D = Hamilton Rating Scale for Depression, POMS = Profile of Mood States.
Within-treatment group changes: [a]$p < .005$. Between-treatment group changes: [b]$p < .05$, [c]$p < .01$, [d]$p < .001$.

tained significantly higher proportions of responders in comparison with the placebo group (sertraline 52%, amitriptyline 51%, and placebo 37%, p = .016 and p = .024, respectively), and that there were no significant differences between the active drug groups.

Patient Ratings

The patient-rated mean POMS Factor 2 (depression/dejection) scores demonstrated a highly significant improvement for sertraline versus placebo at all visits. The amitriptyline-treated group showed significant improvement over the placebo-treated group at Week 3 and the last visit only. Sertraline treatment effected significantly greater improvement than amitriptyline at Weeks 1 and 2 and at the last visit (Table 3). The patient-rated mean POMS Factor 4 (vigor) scores showed significant improvement for sertraline over placebo treatment at Weeks 6, 7, and 8 and at the last visit. For amitriptyline-treated patients, there was significantly greater improvement over placebo recipients at Week 1 and at study exit. Sertraline treatment was associated with greater mean improvement than amitriptyline at all timepoints, but these differences between sertraline and amitriptyline did not attain statistical significance. The patient-rated BDI improved statistically significantly more in both active drug groups than in the placebo group at study exit (p = .001 for sertraline and p = .01 for amitriptyline). There was no significant difference between sertraline and amitriptyline for this measure.

Patient-Rated Quality of Life

Since multiple comparisons were performed, we conducted a principal component analysis to assess the correlations between various items (domains). If domains are interrelated (for example, two different ratings for depression), correction for multiple comparisons may not be required. Since there was significant correlation among domains in quality of life ratings, correction for multiple comparisons was not deemed necessary. Readers interested in a detailed written discussion of this rationale may contact the corresponding author (R.B.L.).

The Q-LES-Q detected significant improvements in mean change from baseline to final visit for both active drug groups over placebo in the physical health, school/course work, social relationships, general activities, medication satisfaction, life satisfaction, and leisure activities scales. Measures of work, household duties, and subjective feeling indicated that the sertraline group, but not the amitriptyline group, was significantly improved compared with placebo. For the subjective feelings, general activities, overall life satisfaction, social relationships, and household duties scales, sertraline recipients showed greater improvements than amitriptyline recipients at all visits; differences were discernible at Week 2 for subjective feelings, household duties, and general activities.

The HRQOL-II demonstrated more variable results. For two scales (health perception and cognitive function), sertraline recipients improved significantly more than placebo recipients at the last visit, but the amitriptyline recipients did not. For three scales (energy/vitality, social interaction, and life satisfaction), both active drug groups were significantly better than placebo at the final visit. Sertraline-associated improvements in social interaction and life satisfaction were greater than those associated with amitriptyline at all timepoints and attained significance at Week 2 for social interaction. For three scales (bed disability days, alertness behavior, and work behavior), both active drug groups demonstrated greater mean improvements than placebo, but these differences did not attain statistical significance. For the home management scale, amitriptyline was significantly better than placebo; sertraline was no different than placebo on this measure.

Table 4. Summary of Analysis of Baseline to Last Visit Changes in Quality of Life Scale Scores, by Treatment Group, in the Intent-to-Treat Population

Scale	p Value (Drug vs Placebo)	
	Sertraline	Amitriptyline
Quality of Life Enjoyment and Satisfaction Questionnaire scales		
Work	< .01	NS
Household duties	< .05	NS
Physical health	< .01	< .01
Subjective feeling	< .01	NS
Leisure activities	< .01	< .01
Social relationships	< .01	< .01
General activities	< .01	< .01
School/course work	< .05	< .05
Medication satisfaction	< .01	< .05
Overall life satisfaction	< .01	< .01
Health-Related Quality of Life battery		
Cognitive function	< .01	NS
Work behavior	NS	NS
Health perception	< .05	NS
Energy/vitality	< .05	< .01
Social interaction	< .01	< .01
Life satisfaction	< .01	< .01
Alertness behavior	NS	NS
Home management	NS	< .05
Bed disability days	NS	NS

Table 4 presents a summary of the analysis of baseline to final visit changes in quality of life domains.

Tolerability of Treatment

Three hundred ninety-two patients were evaluable for safety. The overall incidence of treatment-related adverse events was significantly higher in the amitriptyline recipients (71.8%) than in the sertraline recipients (49.2%; $p < .01$) and placebo recipients (31.8%; $p < .01$). There was no significant difference in the incidence of adverse events between the sertraline and placebo groups. Treatment-related adverse events data are displayed in Table 5.

Amitriptyline recipients dropped out of the study due to adverse events more frequently (15.3%) ($p < .001$) than sertraline (3.8%) or placebo (0.0%) recipients. However, the incidences of discontinuations due to sertraline and placebo treatment-related adverse events were not significantly different from each other. Amitriptyline was associated with a significantly higher frequency of treatment-related dry mouth, somnolence, constipation, increased appetite, and weight gain compared with sertraline. Nausea occurred significantly more frequently in sertraline recipients than in the amitriptyline group. However, there was no difference in the incidence of treatment-related nausea between the sertraline and placebo groups, nor for any other treatment-related adverse events with > 2% incidences. This is in marked contrast to the amitriptyline-treated patients, who had significantly increased incidences of drug-related somnolence, dry mouth, constipation, dyspepsia, and increased appetite compared with placebo-treated patients.

There were some statistically significant, but minor changes in blood pressure and pulse rate, which were not clinically meaningful. Supine diastolic blood pressure increased in amitriptyline recipients in comparison with sertraline and placebo recipients. Sertraline-treated patients showed a small (0.4 bpm) but statistically significant ($p < .05$) decrease in supine pulse rate in comparison with placebo-treated patients.

Over the course of the treatment, amitriptyline-treated patients demonstrated a significant ($p < .01$) mean increase in body weight of 3.8 lb (1.7 kg), compared with patients treated with both placebo (0.6 lb [0.3 kg]) and sertraline (–1.1 lb [0.5 kg]). The small weight loss associated with sertraline treatment was significantly different from placebo ($p < .01$). One amitriptyline recipient and one placebo recipient, but no sertraline recipients, were discontinued due to treatment-emergent ECG abnormalities. One sertraline recipient was discontinued because of modest liver function test increases, and one placebo recipient was discontinued owing to a low platelet count.

DISCUSSION

The main finding of this study was that successful treatment of major depression improves quality of life. As expected, both amitriptyline and sertraline treatment resulted in significantly better antidepressant efficacy than placebo as measured by physician and patient rating scales. This efficacy was consistently observed across variables and was comparable between both active drugs.

The purpose of this study was to extend the usual assessments of efficacy to include the subjective experience of depressed outpatients over the treatment period. In contrast to the physician efficacy assessments, which rated the antidepressants comparably, the patient-assessed depression ratings (POMS Factor 2 and BDI) favored sertraline over amitriptyline throughout the study. This may be a reflection of the inherent bias of most depression rating scales toward conventional antidepressants, in that typical side effects such as sedation, somnolence, and increased appetite/weight gain may be rated as improvements in depression. Antidepressants without these side effects may thus appear (i.e., in rating scales) slower in onset of action or appear to result in smaller improvements as assessed by these rating scales. However, the patient's interpretation of treatment effects such as sedation/somnolence and weight gain may not necessarily be experienced as improvements in depression, but rather as bothersome side effects.

Quality of life evaluations indicate the patient's viewpoint of the global effect of the medication treatment including both positive attributes (i.e., efficacy) and negative effects (i.e., side effects) of treatment. The results of the quality of life scales demonstrated that patients rated

Table 5. Incidence of Treatment-Related Adverse Events[a]

	Sertraline		Amitriptyline		Placebo	
Adverse Event	% Patients	% Who Discontinued Due to the Adverse Event	% Patients	% Who Discontinued Due to the Adverse Event	% Patients	% Who Discontinued Due to the Adverse Event
Headache	9.1	0.0	8.4	0.0	6.2	0.0
Dizziness	5.3	0.0	9.2	1.5	4.7	0.0
Tremor	3.8	0.0	7.6	0.0	2.3	0.0
Dry mouth	16.7	1.5	48.1	0.8**‡	10.9	0.0
Somnolence	10.6	1.5	35.9	9.2**‡	5.4	1.0
Insomnia	6.1	0.0	2.3	0.0	2.3	0.0
Nervousness	3.0	0.0	4.6	1.5	3.1	0.0
Nausea	10.6	0.0	3.1	0.0*†	9.3	0.0
Constipation	3.8	0.0	11.5	0.0*‡	1.6	0.0
Dyspepsia	2.3	0.0	7.6	0.8‡	0.8	0.0
Increased appetite	0.8	0.0	11.5	0.0**‡	1.6	0.0
Fatigue	6.8	0.0	6.9	2.3	3.9	0.0

[a]Adverse events occurring in > 4% patients in at least one group.
*p < .05 vs. sertraline.
**p < .01 vs. sertraline.
†p < .05 vs. placebo.
‡p < .01 vs. placebo.

sertraline therapy as having significant benefits in several areas compared with placebo. These benefits include improvements in cognitive function, general activities, household duties, and work behavior, which suggests the likelihood of an improved ability to perform everyday functions. Improvements in social interactions, overall life satisfaction, subjective feeling, and health perception suggest beneficial changes in outlook as well as mood. In the patient self-rated HRQOL-II scale, more variable results were obtained. This may be due to differences in the scoring on some items such that higher scores on some items (e.g., energy/vitality) indicated increased disability but on other items the higher self-rated scores indicated improvement, leading to confusion in completing this self-rating reported by some patients. Any effect would most likely have been distributed across all the groups. Since this quality of life scale has been shown to be both valid and reliable in its present form,[23] we do not believe that the study results were substantially affected.

It is clear that effective treatment of a major depressive episode is associated with increased quality of life and that these measures were consistent with clinical assessment of improvement in depression. It is conceivable that suboptimal dosing in the amitriptyline group affected subjective quality of life ratings that were not reflected in the efficacy ratings. However, the efficacy measures (HAM-D reduction ≥ 50% and CGI-I of 1 or 2) were nearly identical for the active treatment groups. Also, subjective depression ratings (BDI and POMS) were no different between the two active treatments, both of which were superior to placebo-recipient ratings. Thus, while it cannot be absolutely excluded, it appears unlikely that differences observed in quality of life ratings were due to undetected differences in efficacy between the two active treatment groups. Attention to the quality of life dimension of antidepressant treatment has been lacking in many studies, and our data suggest that these measures may be important in assessing the effectiveness of treatment and may allow for more detailed examination of subjective outcome in antidepressant trials. In particular, longer term evaluation may highlight differences in treatment that are not evident in short-term studies such as this one. Since antidepressant treatment should generally continue for 6 to 12 months, it is clear that a longer term evaluation would be able to provide a more realistic assessment of effects of antidepressant treatment on quality of life.

An important finding in this regard is that sertraline was better tolerated than amitriptyline, as indicated by the lower incidence of adverse events and discontinuations due to adverse events. Amitriptyline adverse events may have more impact on longer term quality of life because of their nature or type and severity, e.g., sedation. Adverse events (of mild-to-moderate severity) associated with sertraline appeared to be better tolerated than those associated with amitriptyline, as reflected by lower discontinuations due to adverse events. Poorly tolerated therapy is more likely to result in poor compliance with its consequences of relapse, recurrence, and depression-associated morbidity and mortality. Financial, psychological, and social costs are also associated with unsuccessful antidepressant therapy, including the discontinuation of one antidepressant medication and initiation of another.[26]

In this flexible dosage design, it is interesting to note that amitriptyline doses were generally maintained at mid–dose range levels. This suggests that the dose of amitriptyline therapy prescribed may have been limited by related adverse events and that a significant proportion of patients could not tolerate the medication and withdrew from the study. It is possible that limitation in upward dose titration of amitriptyline may have resulted in suboptimal dosing and less robust antidepressant effects for some patients. However, this is reflective of problems encountered in the

"real world" of clinical practice. In contrast, sertraline doses were generally nearer the maximum permitted in the study, and despite the higher doses, significantly fewer patients discontinued due to adverse events. There is evidence from a double-blind, fixed-dose study comparing 50-, 100-, and 200-mg doses of sertraline with placebo that 50 mg of sertraline is as effective as higher doses.[27] The fairly high final mean dose of sertraline is probably related to rapid upward dose titration. The well-tolerated side effect profile may have allowed rapid upward titration of sertraline to the maximum dose permitted in many patients before sufficient time for assessment of the need for a dose increase. It could be reasonably argued that selection of a better comparator such as a "user friendly" TCA (desipramine or nortriptyline) may have been a more appropriate choice. Indeed, such comparisons would be informative. However, the continued popularity of amitriptyline in primary care settings (i.e., third most frequently prescribed) suggests that this agent is a clinically relevant choice. Further studies comparing other TCAs (desipramine or nortriptyline) and SSRIs designed to examine treatment outcome from the patient's perspective are warranted.

Finally, although weight gain can be initially desirable for some patients, long-term treatment required to adequately treat depression with TCAs may often be associated with unacceptable weight gain.[28] In the amitriptyline group, mean weight gain of 3.8 lb (1.7 kg) over 8 weeks was noted. While it is difficult to extrapolate from short-term findings, they suggest that continued weight gain may also compromise compliance and treatment satisfaction in patients taking tricyclic antidepressants over the long term. As with the quality of life assessment, long-term controlled studies that more closely represent "real life" clinical practice are needed to assess these effects.

In summary, this study suggests that sertraline therapy offers clinical advantages over amitriptyline treatment in important areas that may influence the patient's ability to tolerate and continue treatment. Benefits in quality of life over amitriptyline for several domains including work, cognitive function, subjective feeling, and health perception were apparent. The findings also suggest that treatment discontinuation, at least in the short term, is significantly greater in the group treated with the conventional tricyclic amitriptyline than with the new serotonin selective agent sertraline. Since long-term treatment (i.e., 6–12 months) is necessary, these data suggest that compliance may be enhanced in patients treated with agents that have a more favorable side effect profile such as sertraline and that successful completion of an adequate course of treatment may be more likely to be achieved.

Drug names: amitriptyline (Elavil and others), chloral hydrate (Noctec), desipramine (Norpramin and others), fluoxetine (Prozac), imipramine (Tofranil and others), nortriptyline (Pamelor and others), sertraline (Zoloft), temazepam (Restoril and others).

REFERENCES

1. Kiloh L, Andrews G, Neilson M. Long-term outcome of depressive illness. Br J Psychiatry 1988;153:752–757
2. Fawcett J. Morbidity of clinical depression. Int Clin Psychopharmacol 1993;8:217–220
3. Lee A, Murray R. Long-term outcome of Maudsley depressives. Br J Psychiatry 1988;153:741–751
4. Agosti V, Stewart J, Quitkin F. Life satisfaction and psychosocial functioning in chronic depression: effect of acute treatment with antidepressant. J Affect Disord 1991;23:35–41
5. Frank E, Kupfer D, Bulik C, et al. Imipramine and weight gain during the treatment of recurrent depression. J Affect Disord 1990;20:165–172
6. Henry JA. A fatal toxicity index for antidepressant poisoning. Acta Psychiatr Scand Suppl 1989;80(suppl 354):37–45
7. Montgomery SA, Baldwin D, Green M. Why do amitriptyline and dothiepin appear to be so dangerous in overdose? Acta Psychiatr Scand Suppl 1989;80(suppl 354):47–53
8. Corruble E, Puech A. How to improve the risk-benefit ratio of antidepressants. Int Clin Psychopharmacol 1993;8:237–241
9. Maj M, Veltro F, Pirozzi R, et al. Pattern of recurrence of illness after recovery from an episode of major depression: a prospective study. Am J Psychiatry 1992;149:795–800
10. Doogan D, Caillard V. Sertraline in the prevention of depression. Br J Psychiatry 1992;160:217–222
11. Kasper S. Rationale for long-term antidepressant therapy. Int Clin Psychopharmacol 1993;8:225–235
12. Cohn CK, Shrivastava R, Mendels J, et al. Double-blind, multicenter comparison of sertraline and amitriptyline in elderly depressed patients. J Clin Psychiatry 1990;51(12, suppl B):28–33
13. Mesters P, Cosyns P, Dejaiffe G, et al. Assessment of quality of life in the treatment of major depressive disorder with fluoxetine, 20 mg, in ambulatory patients aged over 60 years. Int Clin Psychopharmacol 1993;8:337–340
14. Sullivan G, Wells K, Leake B. Clinical factors associated with better quality of life in a seriously mentally ill population. Hospital and Community Psychiatry 1992;8:794–798
15. Jaeschke R, Guyatt GH, Cook D. Quality of life instruments in the evaluation of new drugs. PharmacoEconomics 1992;1(2):84–94
16. Fletcher A, Gore S, Jones D, et al. Quality of life measures in health care, II: design, analysis, and interpretation. BMJ 1992;305:1145–1148
17. IMS America Audited Prescription Data 1990 and 1997. Plymouth Meeting, Pa
18. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
19. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
20. Endicott J, Spitzer RL, Fleiss JL, et al. The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 1976;33:766–771
21. Montgomery SA, Asberg M. A new depression rating scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
22. Endicott J, Nee J, Harrison W, et al. Quality of life enjoyment and satisfaction questionnaire: a new measure. Psychopharmacol Bull 1993;29:321–326
23. Revicki D, Turner R, Brown R, et al. Reliability and validity of a Health-Related Quality of Life battery for evaluating outpatient antidepressant treatment. Qual Life Res 1992;1:257–266
24. McNair DM, Lorr M, Droppleman LF, et al. Profile of Mood States. San Diego, Calif: Educational and Industrial Testing Service; 1971
25. Beck AT, Ward CH, Mendelson M, et al. Inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–571
26. Sclar D, Robison L, Skaer T, et al. Antidepressant pharmacotherapy: economic outcomes in a health maintenance organization. Clin Ther 1994;4:715–729
27. Fabre LF, Abuzzahab FS, Amin M, et al. Sertraline safety and efficacy in major depression: a double-blind fixed-dose comparison with placebo. Biol Psychiatry 1995;38:592–602
28. Agency for Health Care Policy and Research. Clinical Practice Guideline: Depression in Primary Care, vol 2. (AHCPR publication 93-0551). Washington, DC: US Government Printing Office; 1994:56