Psychosocial Outcomes Following Long-term, Double-blind Treatment of Chronic Depression With Sertraline vs Placebo

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Background: Chronic forms of depression are associated with significant functional and psychosocial impairments. To date, no study has measured psychosocial functioning in this population during long-term maintenance antidepressant treatment or following the double-blind discontinuation of treatment.

Methods: Patients with chronic major or double depression completed 12 weeks of short-term treatment followed by 16 weeks of continuation treatment with sertraline hydrochloride. Responders at the end of the continuation phase were randomized, double-blind, to 18 months of maintenance therapy with either sertraline (n=77) or placebo (n=84). Multiple domains of psychosocial functioning were assessed during double-blind therapy.

Results: Substantial worsening in psychosocial function measures occurred in patients taking placebo compared with sertraline during maintenance. Patients with reemergence of depression lost psychosocial gains regardless of treatment. In the subsample of patients who remained in remission throughout maintenance, most of the observed improvement in psychosocial functioning occurred during short-term treatment. By maintenance end point, normalization of functioning was achieved by 58% to 84% of remitters, depending on the outcome measure used.

Conclusions: These results indicate that long-term treatment of chronic forms of depression can result in sustained psychosocial benefits. Discontinuation of treatment results in frequent reemergence of symptoms and loss of psychosocial gains. Long-term treatment resulted in only modest further improvement of psychosocial measures over that achieved in the short-term phase.

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THREE FORMS of chronic unipolar depression have been described: dysthymic disorder, chronic major depression, and double depression, in which dysthymia is punctuated by episodes of major depression. All 3 forms of chronic depression are frequently associated with a significant degree of social and vocational role impairment and academic and vocational underachievement, leading to lost human capital.1-7

Surprisingly, in light of the chronicity of the illness, successful short-term treatment with antidepressant medications results in rapid and marked improvement in social and vocational functioning after only 6 to 12 weeks.6,7 Such findings suggest that the social and vocational role deficits experienced by chronically depressed patients result from treatment-responsive depressive symptoms rather than from ingrained personality traits.

A previous report5 focused on the effect of short-term treatment on psychosocial functioning. This article reports the effect of maintenance-phase treatment on psychosocial outcomes in the same chronically depressed patient sample. The following specific questions are addressed: (1) Is sertraline hydrochloride associated with better psychosocial outcomes than placebo during maintenance treatment of remitted patients with chronic depression? (2) When depression recurs, how extensive is the loss of improvement in psychosocial functioning? (3) Is impairment in psychosocial functioning at maintenance baseline a predictor of subsequent relapse? (4) Are further improvements in psychosocial functioning, beyond those occurring during the short-term phase of treatment, evident during 18 months of maintenance treatment in remitted, depressed patients? (5) To what extent does psychosocial functioning achieve “normal” levels by the end of maintenance treatment in those who remain in remission?
PATIENTS AND METHODS

PATIENTS

Details of inclusion and exclusion criteria and study design are provided in a previous publication.8 Outpatients meeting DSM-III-R criteria for a current episode of chronic major depression (of at least 2 years’ duration) or dysthymic disorder co-occurring with major depression (double depression) were enrolled in this maintenance treatment study if they successfully completed both a 12-week, double-blind short-term phase of treatment and a 16-week, double-blind continuation phase. Patients were eligible for the maintenance phase of the study if they achieved and sustained at least a satisfactory antidepressant response as operationally defined by the following criteria: (1) not meeting DSM-III-R criteria for major depression; (2) a 24-item Hamilton Depression Scale (HAM-D) total score of 13 or less; (3) Clinical Global Impression (CGI) severity score of 3 or less; (4) CGI improvement score of 2 or less; and (5) successful completion and compliance with 28 weeks of short-term and continuation treatment.

STUDY DESIGN

The maintenance study was approved by the institutional review boards at each of the 12 collaborating centers. The benefits and risks of study participation were reviewed with each patient. A separate, written informed consent was obtained for the maintenance phase of the study. The design of the maintenance phase of the study consisted of random, double-blind assignment to parallel groups for 76 weeks of treatment with either sertraline hydrochloride (flexible dose of 50-200 mg/d) or placebo. Patients randomized to placebo were tapered off sertraline via placebo substitution at a 50-mg/wk rate of reduction. Randomization was stratified by high and low probability of recurrence based on 2 variables hypothesized to predict increased probability of recurrence: presence of residual depressive symptoms (defined as a HAM-D score of ≥10 and a CGI severity score of 3 at the end of the continuation treatment) and history of 2 or more prior major depressive episodes. Note that the 24-item HAM-D scale was used to be consistent with previous chronic depression studies and because it more fully captures the range of symptoms often associated with chronic forms of depressive illness. Patients were evaluated and rated every 2 weeks for the first 12 weeks and then monthly thereafter. If patients’ depression worsened, visit frequency could be increased to once per week.

DEFINITION OF EXACERBATIONS AND RECURRENTS

Definition and management of depression exacerbations and recurrences are detailed in previous reports.8,9 Briefly, patients were considered to have an impending recurrence if, at either a scheduled or unscheduled assessment visit, they met the following criteria: (1) DSM-III-R criteria for major depression for at least 3 weeks; (2) CGI severity score of 4 or higher (at least moderate severity); (3) CGI improvement score of 3 or higher (minimally improved or less); and (4) an increase in HAM-D score of 4 or more points over maintenance-phase study baseline. Such patients were rescheduled for a second visit within 1 week (total duration of clinical worsening criteria of at least 4 weeks) and were declared to have had a recurrence if they continued to meet these criteria and a senior investigator who interviewed the patient judged the patient to be in a major depressive episode.

Three time-to-event variables were primary end points of the maintenance treatment study8,9: time to recurrence of a major depressive episode, time to reemergence of clinically significant depression, and time to reemergence of first symptoms of depression. Time to reemergence of clinically significant depression and time to reemergence of first symptoms of depression were determined by a blinded review by a panel of 6 senior investigators of the HAM-D, CGI, and overall clinical picture of all patients who discontinued the study prematurely. Agreement among 6 of the 8 senior investigators (75%) was required for a patient to be categorized as having met either of these 2 clinical end points.

PSYCHOSOCIAL FUNCTION ASSESSMENTS

Scales to assess psychosocial function included the Social Adjustment Scale–Self Report (SAS-SR), the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36),...
and the Longitudinal Interval Follow-up Evaluation (LIFE). The SAS-SR, developed by Weissman and Bothwell,10 is the most widely used measure of social adjustment in depressed patients. The scale is composed of 8 subscales and a total adjustment score. For this study, we evaluated changes on the composite total of all 8 subscales. In the maintenance phase of the study, the SAS-SR was administered at the maintenance baseline (which consisted of the last visit of the continuation phase) and weeks 24, 52, and 76 or when a patient discontinued the study if before week 76.

The SF-3611 is a self-report, health-related, quality-of-life measure designed to assess overall health status and functioning. Its 8 subscales assess physical functioning, role limitations owing to physical health problems, bodily pain, general health, energy and fatigue, social functioning, role limitations owing to emotional problems, and mental health. The SF-36 has been used extensively in general population surveys and in the Medical Outcomes Study.4 In assessing psychosocial outcomes, we focused on the social function and role limitations subscales. The SF-36 was administered at the maintenance baseline and at weeks 8, 24, 52, and 76 or when a patient discontinued the study if before week 76.

The LIFE12 is an assessment of symptoms and psychosocial functioning with demonstrated reliability and validity. It has been used in several large-scale, prospective, longitudinal studies of psychiatric patients. We report results on items from the LIFE that assessed overall psychosocial functioning (interviewer and patient rated) and life satisfaction. Raters from all sites were trained to administer the LIFE by the developers of the scale before beginning the study. The LIFE was administered at maintenance baseline and at weeks 16, 32, 48, 64, and 76 or when a patient discontinued the study if before week 76. The source of data on employment was the SAS-SR, and the source of data on time worked per week is the LIFE.

GENERAL POPULATION SAMPLES

To provide a normative reference for the level of psychosocial function, we compared SAS-SR and SF-36 scores of our sample with previously reported community samples of the general population.13,14 Although these “between-study” comparisons are necessarily limited by differences in time, location, demographics, and methods of administration, they provide an approximate frame of normative reference that is useful for gauging psychosocial function. The demographic characteristics of our chronically depressed sample approximated the normative samples reported previously.14,15

STATISTICAL ANALYSES

The treatment sample analyzed in this report consists of the patients originally randomized to sertraline in the short-term study and rerandomized to sertraline or placebo in the maintenance study. Descriptive statistics are presented for psychosocial measures at short-term baseline, short-term end point (week 12), maintenance baseline, and maintenance end point. Maintenance end point is defined as the last available measure for patients who discontinued the study early or week 76 for completers. In the event of early discontinuation, the last observed value is carried forward. Group comparisons at maintenance baseline for psychosocial measures are from an analysis of variance model with adjustments for 3 stratification variables: study site (pooled into 4 groups), depression type, and probability of recurrence. Because of the small number of patients at some study sites, the 12 sites were pooled into 4 groups based on size. Similar comparisons for change from maintenance baseline to maintenance end point are from an analysis of covariance model with adjustments for study site, depression type, probability of recurrence, and maintenance baseline value. Change from maintenance baseline to maintenance end point within groups was assessed with a 1-sample t test for continuous data and the McNemar test for categorical data. Comparisons of psychosocial measures vs the normative community sample were performed using a 2-sample t test. The relationships between the HAM-D and SAS-SR total scores were estimated with the Pearson correlation coefficient.

All tests are 2-sided. P <.05 was considered statistically significant. The evaluation of psychosocial outcomes in the maintenance protocol is a secondary analysis and is largely exploratory in nature. Therefore, P values are best interpreted as descriptive statistics that identify differences between groups rather than confirm hypotheses that such differences exist. Given this exploratory framework, P values were not adjusted for multiple comparisons.

depression, with a mean±SD age of onset of 24.7±12.1 years. The mean±SD age of onset of dysthymia was 16.2±13.2 years. Compared with the original cohort undergoing the short-term treatment, maintenance patients tended to be better educated (40% college graduates) and more likely to be married (45% married) than those originally randomized to sertraline and not entering maintenance treatment.13

PSYCHOSOCIAL OUTCOMES DURING MAINTENANCE TREATMENT

As reported previously,9 maintenance-phase sertraline treatment resulted in significantly better outcome than placebo by all criteria used, including depression recurrence (6% vs 23%; P = .004) and reemergence of depressive symptoms (26% vs 50%; P = .001). In the current analysis, no significant differences in psychosocial measures were found at maintenance baseline for either treatment group (Table 1). Consistent with the significantly higher depression recurrence rates for placebo noted herein,9 psychosocial measures exhibited statistically significant worsening in patients who had been randomized to placebo compared with patients maintained with sertraline.

One of the most surprising findings from the short-term phase of the current study was the speed with which psychosocial functioning improved during short-term treatment in patients with a mean current major depression duration of 6 years.6 In the current analysis (Table 2), patients who had a depression reemergence during the maintenance phase of the study had a significant worsening in their psychosocial functioning (except for the SF-36 physical role factor), losing essentially all of the improve-
ment they had gained in response to treatment. The magnitude of the loss of psychosocial functioning in patients with reemergence was similar whether the treatment was sertraline or placebo.

There was no significant difference in psychosocial functioning from maintenance baseline to end point for patients who remained healthy (Table 2). However, patients taking sertraline who remained healthy showed sustained or modest improvement in the LIFE scores, whereas patients taking placebo showed some decline in their LIFE scores. As a result (Table 2), there was a significant difference at maintenance end point for sertraline vs placebo in the groups that remained healthy. The correlation between depression severity and psychosocial functioning was high for sertraline (week 76 correlation between HAM-D total and SAS-SR total, 0.72; \( P = .001 \)), but it was weaker for patients taking placebo (week 76 correlation between HAM-D total and SAS-SR total, 0.24; \( P = .31 \)).

We were interested to know whether there were differences in psychosocial functioning at maintenance baseline for the subset of sertraline-treated patients who had a depression reemergence (\( n = 20 \)) vs sertraline-treated patients who remained depression-free (\( n = 57 \)). The results of this exploratory analysis (Table 2) found significantly worse maintenance baseline LIFE scores (by interviewer assessment) for patients who eventually relapsed (2.25 ± 0.91) compared with patients who remained healthy (1.65 ± 0.84; \( P = .02 \)). There were no significant maintenance baseline differences between the 2 outcome groups on the other measures we evaluated.

An analysis of the subgroup of sertraline-treated patients whose depressions remained in remission throughout the maintenance phase of the study revealed that less than 5% of the overall improvement (from short-term baseline) in SAS-SR total and LIFE interviewer assessment scores occurred during the maintenance phase of the study. There was no statistically significant further improvement on any psychosocial measure from maintenance baseline to maintenance end point.

We compared scores for the sertraline-treated patients who remained in remission at maintenance end point with community samples for the SAS-SR and the social function score. (REPRINTED) ARCH GEN PSYCHIATRY/VOL 59, AUG 2002 WWW.ARCHGENPSYCHIATRY.COM

## Table 1. Effect of Maintenance-Phase Treatment With Sertraline vs Placebo on Psychosocial Measures Among All Randomized Maintenance-Phase Patients

| Psychosocial Measure | Maintenance-Phase Baseline | | | | | Maintenance-Phase End Point | | | | | | | Sertraline Hydrochloride | Placebo | Sertraline Hydrochloride | Placebo |
|----------------------|---------------------------|---|---|---|---|---------------------------|---|---|---|---|---|---|---|---|
|                      | (n = 77)                  | (n = 84) | (n = 77) | (n = 84) | (n = 77) | (n = 84) | (n = 77) | (n = 84) | (n = 77) | (n = 84) | (n = 77) | (n = 84) | (n = 77) | (n = 84) |
| SAS-SR total score   | 1.75 (0.38)               | 1.83 (0.39) | 1.87 (0.52) | 2.16 (0.59)† | 1.75 (0.38) | 1.83 (0.39) | 1.87 (0.52) | 2.16 (0.59)† |
| SF-36 social function score | 90.8 (12.9) | 88.8 (17.0) | 80.6 (22.0) | 68.9 (28.1)† | 90.8 (12.9) | 88.8 (17.0) | 80.6 (22.0) | 68.9 (28.1)† |
| SF-36 role emotional score | 79.5 (34.2) | 80.1 (32.7) | 65.7 (41.8) | 45.0 (44.1)† | 79.5 (34.2) | 80.1 (32.7) | 65.7 (41.8) | 45.0 (44.1)† |
| SF-36 role physical score | 81.1 (32.5) | 79.8 (30.8) | 74.3 (36.4) | 72.2 (40.4) | 81.1 (32.5) | 79.8 (30.8) | 74.3 (36.4) | 72.2 (40.4) |
| LIFE subject assessment score | 1.95 (0.77) | 2.11 (0.71) | 2.27 (1.23) | 3.08 (1.17)§ | 1.95 (0.77) | 2.11 (0.71) | 2.27 (1.23) | 3.08 (1.17)§ |
| LIFE interviewer assessment score | 1.82 (0.90) | 1.94 (0.87) | 2.23 (1.14) | 3.00 (1.11)§ | 1.82 (0.90) | 1.94 (0.87) | 2.23 (1.14) | 3.00 (1.11)§ |
| LIFE satisfaction score | 1.93 (0.73) | 2.11 (0.67) | 2.24 (1.08) | 2.99 (1.06)§ | 1.93 (0.73) | 2.11 (0.67) | 2.24 (1.08) | 2.99 (1.06)§ |

*Data are given as mean (SD). Sample sizes vary because of sporadic missing data. SAS-SR indicates Social Adjustment Scale–Self Report; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; and LIFE, Longitudinal Interval Follow-up Evaluation.
†\( P < .02 \) for differences between sertraline and placebo groups for change during maintenance.
‡\( P < .005 \) for differences between sertraline and placebo groups for change during maintenance.
§\( P < .001 \) for differences between sertraline and placebo groups for change during maintenance.

## Table 2. Psychosocial Measures From Maintenance Baseline to End Point Based on Depression Outcome for All Randomized Maintenance-Phase Patients

| Psychosocial Measure | Maintenance Baseline | | | | | Maintenance End Point | | | | | | | Sertraline Hydrochloride | Placebo | Sertraline Hydrochloride | Placebo |
|----------------------|-----------------------|---|---|---|---|-----------------------|---|---|---|---|---|---|---|---|
|                      | DR (n = 20)           | SW (n = 57) | DR (n = 42) | SW (n = 42) | DR (n = 20) | SW (n = 57) | DR (n = 42) | SW (n = 42) | (n = 84) | (n = 77) | (n = 84) | (n = 77) |
| SAS-SR total score   | 1.73 (0.36)           | 1.76 (0.39) | 1.84 (0.40) | 1.82 (0.39) | 2.34 (0.49)† | 1.71 (0.42)§ | 2.49 (0.56)‡ | 1.77 (0.34)§ |
| SF-36 social function score | 90.3 (11.5) | 90.9 (13.4) | 87.1 (18.9) | 90.4 (14.7) | 59.0 (22.2)‡ | 88.0 (16.5)‡ | 51.7 (25.8)‡ | 88.7 (14.7)§ |
| SF-36 emotional role score | 83.3 (32.2) | 78.4 (35.0) | 82.5 (29.7) | 77.3 (35.7) | 20.4 (36.4)‡ | 81.1 (31.0)§ | 17.1 (31.7)‡ | 74.4 (35.4)§ |
| SF-36 physical role score | 78.1 (37.5) | 81.9 (31.3) | 74.8 (36.2) | 85.0 (23.2) | 58.3 (41.1)† | 79.8 (33.2)‡ | 54.9 (45.8)‡ | 90.4 (22.7)§ |
| LIFE subject assessment score | 2.20 (0.77) | 1.86 (0.75) | 2.17 (0.76) | 2.05 (0.65) | 3.65 (1.22)‡ | 1.83 (0.85)§ | 3.83 (0.83)§ | 2.24 (0.69)§ |
| LIFE interviewer assessment score | 2.25 (0.91) | 1.65 (0.84) | 1.95 (0.79) | 1.92 (0.96) | 3.65 (1.06)‡ | 1.77 (0.72)§ | 3.69 (0.90)‡ | 2.22 (0.70)§ |
| LIFE satisfaction score | 2.00 (0.56)           | 1.91 (0.77) | 2.17 (0.66) | 2.05 (0.69) | 3.53 (1.01)‡ | 1.83 (0.73)§ | 3.63 (0.77)‡ | 2.27 (0.87)§ |

*Data are given as mean (SD). Sample sizes vary because of sporadic missing data. DR indicates depression reemergence; SW, stayed well; SAS-SR, Social Adjustment Scale–Self Report; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; and LIFE, Longitudinal Interval Follow-up Evaluation.
†Significant (\( P < .05 \)) difference for DR vs SW at maintenance baseline.
‡Significant (\( P < .05 \)) change from maintenance baseline to maintenance end point.
§Significant (\( P < .05 \)) difference for the within-treatment-group comparison of DR vs SW change scores.
||Significant (\( P < .05 \)) difference for the between-treatment-group (sertraline vs placebo) comparison of SW change scores.

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tioni ng, emotional role, and physical role subscales of the SF-36. Patients were considered to have achieved normative levels of functioning on a measure if they were no more than 10% worse than community means (ie, no more than 10% of community norms for the SAS-SR total score and no less than 10% of the mean for the SF-36 scores). Most remitted patients were at or above community levels of functioning at the baseline of the maintenance phase of the study, and they maintained this level of functioning through the end of the maintenance phase.

For sertraline-treated patients, the SAS-SR total score improved at maintenance baseline among patients who remained in remission. There were no significant differences found for maintenance baseline to maintenance end point for all assessments. Normative is defined as no more than 10% worse than the community mean. SAS-SR indicates Social Adjustment Scale–Self Report; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; LIFE, Longitudinal Interval Follow-up Evaluation; and ellipses, data not applicable. Sertraline was given as sertraline hydrochloride.

To our knowledge, this is the first report of the effects of long-term treatment on the psychosocial functioning of patients with chronic depression. We found only modest additional improvement in psychosocial measures compared with the rapid improvement noted at the completion of the short-term treatment phase. Nonetheless, maintenance treatment ensured that initial gains were sustained. In contrast, discontinuation of sertraline use, by double-blind substitution of placebo, resulted in a rapid decline in psychosocial function back to pretreatment levels.

There has been some suggestion in the literature that patients who achieve normative levels of psychosocial functioning may be at lower risk for depression relapse than patients who do not achieve comparable psychosocial recovery. The results of the current study provide only weak support for an association between lack of psychosocial recovery and relapse (Table 2). In fact, the only psychosocial measure that was significantly less improved at maintenance baseline among patients who progressed to depression reemergence during the maintenance phase of the study was the LIFE interviewer assessment score.

Similarly, the LIFE (Table 2) detects a small but significant difference in favor of sertraline among the sub-

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<th>Psychosocial Measure</th>
<th>Short-term Baseline</th>
<th>Short-term End Point</th>
<th>Maintenance Baseline</th>
<th>Maintenance End Point</th>
<th>Overall Improvement During Maintenance Treatment, %</th>
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*Sample sizes may vary because of sporadic missing data. LIFE indicates Longitudinal Interval Follow-up Evaluation; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey. Sertraline was given as sertraline hydrochloride.
group of patients who remained healthy in terms of symptom criteria. This result parallels data from a recent report that found placebo responders in a panic study to have significantly reduced quality-of-life improvement than responders treated with sertraline who achieved equivalent levels of improvement.

If there is only modest incremental improvement in psychosocial indices during longer-term treatment, to what extent is this because patients who have already achieved normative levels of functioning compared with individuals in the community? Using psychosocial functioning scores within 10% of established community norms as a criterion level, this was only partially true. Normative levels of psychosocial functioning had been achieved at maintenance baseline (Table 3) by between 60% and 92% of patients, depending on the psychosocial measure that was examined. In fact, some scales (eg, SF-36 role physical and social functioning; Table 3) show modest declines during maintenance treatment. The presence of persistent psychosocial impairments, despite symptomatic improvement and long-term therapy, suggests that this subset of patients might benefit from specific psychosocial interventions designed to foster more complete rehabilitation.

Perhaps the most notable limitation of the current study consists of the reliance on subjective psychosocial and functional outcome measures. In the current study, there is a relatively high correlation at end point between psychosocial measures and the HAM-D score. Correlations between symptom-based psychosocial scales tend to be lower at baseline, and (as noted herein) there have been reports that placebo responders (based on symptom criteria) show significantly less improvement on psychosocial measures than do responders to active drug. Both of these findings suggest that psychosocial measures are tapping an outcome domain that is, to a certain extent, independent of depression symptom severity as measured by the HAM-D. Nonetheless, more “objective” measures of functioning might be preferable and attempts should be made to include them in future studies. These might include both systematic ratings from significant others and actual measures of behavioral activity (eg, acometers), job attendance, and productivity. Use of in vivo behavioral and work measures in place of current surrogate markers (such as the LIFE and the SAS-SR) may be ideal but is often impractical and may raise confidentiality and other issues relating to the Americans With Disabilities Act.

Another limitation of the study consists of the significant degree of attrition during the treatment. Even though the rate of attrition was what was expected during such a long study, it may have introduced some unspecified bias that might serve to reduce the generalizability of the results.

Finally, the magnitude of the treatment effect observed on the one clinician-rated psychosocial measure (the LIFE) was higher than for the patient-rated measures (the SAS-SR and the SF–36). This parallels the results for depression symptom ratings across most treatment studies and raises the issue of whether adverse effect cueing may have partially abrogated the blind. In our estimation, this is less likely in the current study since the adverse event rate was relatively low at this stage of long-term treatment. In conclusion, this study provides evidence that long-term treatment of chronic forms of depression can result in sustained psychosocial benefits that lead to normalized psychosocial functioning in approximately two thirds of remitted patients.

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