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

James H. Kocsis, MD; Alan Schatzberg, MD; A. John Rush, MD; Daniel N. Klein, PhD; Robert Howland, MD; Leah Gniwesch, PhD; Sonia M. Davis, DrPH; Wilma Harrison, MD

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.

Arch Gen Psychiatry. 2002;59:723-728

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.5-7 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 report6 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 had 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) 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 RECURRENCES

Definition and management of depression exacerbations and recurrences are detailed in previous reports.6,7 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 study:8-10 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 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.

RESULTS

DEFINITIONS OF SAMPLES FOR THE CURRENT ANALYSES

Of the 635 patients who were enrolled in the original short-term phase of the study, 426 were randomized to sertraline and 209 to imipramine hydrochloride. Among the 209 sertraline responders in the short-term phase who began the 4-month continuation phase, 179 patients completed the continuation phase, 169 completed and met criteria for remission or satisfactory response in the opinion of the investigator, and 161 (95%) enrolled in the maintenance treatment trial. These 161 patients, randomly assigned at maintenance baseline to receive either sertraline (n = 77) or placebo (n = 84), constitute the intent-to-treat sample for comparative assessment of psychosocial outcomes. Fifty-seven percent were identified as having a high probability of recurrence. Of the 161 randomized patients, 55 patients completed 76 weeks of maintenance treatment and remained in remission based on consensus criteria (sertraline, n = 33; placebo, n = 22). Reasons for discontinuation included, for sertraline and placebo, respectively, insufficient response (11 vs 34), adverse events or intercurrent illness (8 vs 3), and protocol violation or lost to follow-up (23 vs 23).

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE SAMPLES

The demographic and clinical characteristics of the maintenance-phase study patients have been detailed in previous publications.8 Briefly, 66% were women, with a mean ± SD age of 41.6 ± 9.4 years, and 53% had double

©2002 American Medical Association. All rights reserved.

Downloaded From: https://archpsyc.jamanetwork.com/ by a Non-Human Traffic (NHT) User on 04/19/2019
sive symptoms (26% vs 50%; \(P = .004\)) 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-
The magnitude of the loss of psychosocial functioning in patients with reemergence was similar whether the treatment was sertraline 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 two 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 func-
COMMENT

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-

Table 3. Course of Psychosocial Improvement Among Subgroup of 55 Patients Treated With Sertraline Who Remained in Remission During the Entire Maintenance Phase

<table>
<thead>
<tr>
<th>Psychosocial Measure (Community Mean)</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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (Normative, %)</td>
<td>Mean (Normative, %)</td>
<td>Mean (Normative, %)</td>
<td>Mean (Normative, %)</td>
<td></td>
</tr>
<tr>
<td>SAS-SR total score (1.59)</td>
<td>2.50 (5)</td>
<td>1.76 (56)</td>
<td>1.75 (60)</td>
<td>1.71 (58)</td>
<td>5.1</td>
</tr>
<tr>
<td>SF-36 social functioning score (82.7)</td>
<td>51.6 (24)</td>
<td>90.0 (87)</td>
<td>92.8 (92)</td>
<td>89.7 (84)</td>
<td>-9.0</td>
</tr>
<tr>
<td>SF-36 emotional role score (80.8)</td>
<td>20.0 (5)</td>
<td>81.2 (69)</td>
<td>84.9 (75)</td>
<td>83.0 (67)</td>
<td>-4.0</td>
</tr>
<tr>
<td>SF-36 physical role score (84.2)</td>
<td>65.0 (45)</td>
<td>88.2 (73)</td>
<td>86.8 (70)</td>
<td>83.8 (74)</td>
<td>-17.6</td>
</tr>
<tr>
<td>LIFE subject assessment score</td>
<td>4.09</td>
<td>1.91</td>
<td>1.80</td>
<td>1.82</td>
<td>-1.8</td>
</tr>
<tr>
<td>LIFE interviewer assessment score</td>
<td>3.95</td>
<td>1.91</td>
<td>1.85</td>
<td>1.84</td>
<td>0.9</td>
</tr>
<tr>
<td>LIFE satisfaction score</td>
<td>3.69</td>
<td>1.89</td>
<td>1.85</td>
<td>1.89</td>
<td>-3.3</td>
</tr>
</tbody>
</table>

*Sample sizes vary because of sporadic missing data. No significant differences were 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.

Table 4. Course of Improvement in Work-Related Indexes During Long-term Sertraline Use in Subgroup of 55 Patients Who Remained in Remission During the Entire Maintenance Phase

<table>
<thead>
<tr>
<th>Psychosocial Measure</th>
<th>Short-term Baseline</th>
<th>Short-term End Point</th>
<th>Maintenance Baseline</th>
<th>Maintenance End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients employed, %</td>
<td>83</td>
<td>91</td>
<td>96</td>
<td>98</td>
</tr>
<tr>
<td>Patients with no missed work days in past 2 weeks, %</td>
<td>66</td>
<td>89</td>
<td>88</td>
<td>87</td>
</tr>
<tr>
<td>Hours worked per week, mean (SD)</td>
<td>29.5 (22.1)</td>
<td>37.5 (13.3)</td>
<td>37.2 (15.0)</td>
<td>41.6 (16.6)†</td>
</tr>
<tr>
<td>LIFE, degree of work impairment, mean (SD)</td>
<td>3.0 (1.1)</td>
<td>1.5 (0.6)</td>
<td>1.4 (0.6)</td>
<td>1.5 (0.7)</td>
</tr>
<tr>
<td>SF-36 role physical score, mean (SD)</td>
<td>65.0 (39.0)</td>
<td>88.2 (23.0)</td>
<td>86.8 (23.8)</td>
<td>83.8 (31.2)</td>
</tr>
</tbody>
</table>

*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.

tioning, emotional role, and physical role subscales of the SF-36 (Table 3). 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 remained significantly higher (worse) when compared with the community sample throughout all phases of study treatment. The SF-36 emotional role and physical role were not significantly different from the community sample at the end point of the short-term phase and at the baseline and end point of the maintenance phase of the study. However, the SF-36 social functioning was significantly better than the community sample at these 3 time points.

An analysis of the subset of sertraline-treated patients who remained in remission throughout the maintenance phase of the study (Table 4) revealed that improvements in psychosocial measures were paralleled by improvements in work-related functioning, with most of the improvement also occurring during the short-term phase, including reductions in unemployment and improvements in work attendance.
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 long-term treatment, to what extent is this because patients 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.

Another limitation of the 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 reports7 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, acetometers), 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.

Submitted for publication August 13, 1999; final revision received September 26, 2001; accepted October 1, 2001.

This study was supported by a grant from Pfizer Inc. Drs Howland, Kocsis, and Rush are on the Speaker’s Bureau of Pfizer Inc. Drs Schatzberg and Kocsis are consultants for Pfizer Inc. Dr Schatzberg owns stock in Pfizer Inc. Drs Rush and Kocsis have received research grants from Pfizer Inc.

Corresponding author and reprints: James H. Kocsis, MD, New York Hospital-Cornell Medical Center, Box 140, 525 E 68th St, New York, NY 10021 (e-mail: jhk2002@med.cornell.edu).

REFERENCES


©2002 American Medical Association. All rights reserved.

Downloaded From: https://archpsyc.jamanetwork.com/ by a Non-Human Traffic (NHT) User on 04/19/2019