ORIGINAL ARTICLE

Sertraline for Prevention of Depression Recurrence in Diabetes Mellitus

A Randomized, Double-blind, Placebo-Controlled Trial

Patrick J. Lustman, PhD; Ray E. Clouse, MD; Billy D. Nix; Kenneth E. Freedland, PhD; Eugene H. Rubin, MD, PhD; Janet B. McGill, MD; Monique M. Williams, MD; Alan J. Gelenberg, MD; Paul S. Ciechanowski, MD; Irl B. Hirsch, MD

Context: In patients with diabetes mellitus, depression is a prevalent and recurrent problem that adversely affects the medical prognosis.

Objective: To determine whether maintenance therapy with sertraline hydrochloride prevents recurrence of major depression in patients with diabetes.

Design: A randomized, double-blind, placebo-controlled, maintenance treatment trial. Patients who recovered from depression during open-label sertraline treatment continued to receive sertraline (n=79) or placebo (n=73) and were followed up for up to 52 weeks or until depression recurred.

Setting: Outpatient clinics at Washington University, St Louis, Mo, the University of Washington, Seattle, and the University of Arizona, Tucson.

Patients: One hundred fifty-two patients with diabetes (mean age, 52.8 years; 59.9% female; 82.9% with type 2 diabetes) who recovered from major depression (43.3% of those initially assigned) during 16 weeks of open-label treatment with sertraline (mean dose, 117.9 mg/d).

Intervention: Sertraline continued at recovery dose or identical-appearing placebo.

Main Outcome Measures: The primary outcome was length of time (measured as the number of days after randomization) to recurrence of major depression as defined in *DSM-IV*. The secondary outcome was glycemic control, which was assessed via serial determinations of glycosylated hemoglobin levels.

Results: Sertraline conferred significantly greater prophylaxis against depression recurrence than did placebo (hazard ratio=0.51; 95% confidence interval, 0.31-0.85; *P*=.02). Elapsed time before major depression recurred in one third of the patients increased from 57 days in patients who received placebo to 226 days in patients treated with sertraline. Glycosylated hemoglobin levels decreased during the open treatment phase (mean±SD glycosylated hemoglobin level reduction, –0.4%±1.4%; *P*=.002). Glycosylated hemoglobin levels remained significantly lower than baseline during depression-free maintenance (*P*=.002) and did not differ between treatment groups (*P*=.90).

Conclusions: In patients with diabetes, maintenance therapy with sertraline prolongs the depression-free interval following recovery from major depression. Depression recovery with sertraline as well as sustained remission with or without treatment are associated with improvements in glycosylated hemoglobin levels for at least 1 year.

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CLINICAL DEPRESSION IS present in 1 of every 4 patients with type 1 or type 2 diabetes mellitus.[1] The psychiatric illness lessens quality of life, diminishing the capacity for pleasure and ability to function. It imposes additional risks for hyperglycemia,[2] diabetes complications,[3,4] and mortality.[5,6] The adverse outcomes are in part related to the important association of depression with the acceleration of coronary heart disease.[3]

The efficacies of psychotherapy and pharmacotherapy for depression in diabetes were examined in earlier randomized controlled trials[7-9] in which treatment was provided over 8 to 16 weeks and then discontinued. Treatment produced significant improvements in both mood and glycemic control, but these benefits, particularly those that accompanied depression remission with antidepressant medication, appeared short lived.[7,8,10,11] As few as 40% of patients with both depression and diabetes remained well in the year following successful depression treatment,[11] 1 in 7 had chronic depression that was unresponsive to available treatments,[4] and recurrence of depression generally was accompanied by a deterioration in glycemic control.[10,11] Additionally, improvement in mood and glycemia may not occur in parallel, and effective antidepressant pharmacotherapy may be ac-

Author Affiliations are listed at the end of this article.

companied by weight-dependent or weight-independent hyperglycemic effects.[7,12]

The efficacy of maintenance antidepressant pharmacotherapy has been demonstrated in placebo-controlled trials of patients receiving psychiatric care, with maintenance treatment reducing depression recurrence by approximately 15% to 30%.[13-18] Unfortunately, patients with medical comorbidity including diabetes typically were excluded from participating in these trials,[19,20] and the course, cause, and treatment responsiveness of depression in diabetes may differ from that in psychiatric samples, making generalization unsafe.[10,11,21] The aim of our study was to determine whether maintenance treatment with sertraline hydrochloride prevents recurrence of comorbid depression in diabetes and influences the longer-term course of glycemic control.

METHODS

OVERVIEW OF STUDY DESIGN

The purpose of the study was to determine whether maintenance therapy with sertraline hydrochloride prevents recurrence of major depression in patients with diabetes. Time to recurrence of major depression was the primary outcome measure, and we hypothesized that this interval would be significantly longer in patients who continued to receive sertraline compared with those who continued to receive placebo. The study was a 2-phase depression treatment trial. In phase 1 (induction), patients with major depressive disorder received up to 16 weeks of open-label treatment with sertraline. In phase 2 (maintenance), those who achieved recovery from depression were randomized to either sertraline or placebo and were followed for up to 52 weeks or until depression recurred. Dovetailing of induction and maintenance medications at the initiation of the maintenance phase allowed blinded tapering for subjects randomized to placebo. Following the dovetailed period, those randomized to sertraline continued to receive the final induction dosage throughout maintenance.

PATIENT SAMPLE

Patients were recruited from March 4, 1998, through February 2, 2004, via advertisements in public media or by referral from university-based diabetes educators and physicians. The study was a collaboration of Washington University, St Louis, Mo, the University of Arizona, Tucson, and the University of Washington, Seattle, with Washington University being the primary site that provided 78.3% of the enrolled subjects. Treatment of patients within this study was completed by July 1, 2004. To enter the induction phase, patients were required to be 18 to 80 years of age, have type 1 or type 2 diabetes and major depressive disorder as defined in *DSM-IV*,[22] and have a total score of 14 or greater on the Beck Depression Inventory (BDI)[23] or 15 or greater on the Hamilton Depression Rating Scale (HDRS).[24] Patients excluded from participation were those with active suicidal or homicidal ideation, a history of attempted suicide, current alcohol or other substance abuse disorders, a history of bipolar depression or any psychotic disorder, or a medical contraindication to sertraline treatment. Patients receiving an antidepressant at the time of study enrollment were tapered off of that medication over an interval of 2 weeks or less while sertraline was introduced. Informed consent to participate was obtained from all of the patients prior to undergoing the medical and psychiatric evaluations. The study was reviewed and approved by the institutional review board at each of the study sites.

Of the 389 patients evaluated for inclusion in the study, 351 (90.2%) satisfied all of the eligibility requirements, were enrolled in the study, and began receiving open treatment with 50 mg/d of sertraline administered in the morning. The dosage was adjusted to a maximum of 200 mg/d depending on adverse effects and clinical response. Treatment was administered by physician assistants or nurse practitioners and guided by the clinical management manual used in the National Institute of Mental Health Treatment of Depression Collaborative Research Program.[25] Initial sessions lasted 45 to 60 minutes, and subsequent sessions lasted 15 to 30 minutes. Recovery from depression was defined per *DSM-IV* criteria as a period of at least 2 months during which there were no significant symptoms of depression,[22] which was defined operationally as 4 consecutive twice-monthly BDI scores of 9 or less within 4 months of beginning sertraline treatment and subsequent confirmation of the absence of major depression by diagnostic reevaluation. The subjects, methods, and outcomes of the open-label induction phase will be described in detail in a separate article and are summarized in the opening section of our "Results" section to the extent necessary to enable readers to evaluate the maintenance phase outcomes.

This article focuses on the 152 patients (43.3% of those enrolled) who recovered from the index episode of depression during the induction phase, including 119 patients (78.3%) from the primary study site. There were no significant differences between sites in patient demographic characteristics including age, sex, race (white vs nonwhite), marital status, and type of diabetes ($P>.11$ for each characteristic). Subjects entering maintenance from the secondary sites had received an additional year of education (mean education, 14.9 vs 13.9 years; $t=-2.0$; $P=.05$).

STUDY DESIGN

Patients who recovered from depression (n=152) were randomly assigned to double-blind, maintenance-phase antidepressant treatment with sertraline (continued at recovery dosage) or placebo through a blinded taper and were followed up for 12 months or until depression recurred. Patients were randomized using a computer-generated algorithm. Randomization was stratified according to site in blocks of 50 numbers such that each block comprised 25 patients randomly assigned to sertraline and 25 to placebo. Each patient was assigned the next sequential number for the particular center. Administration of treatment and all of the study evaluations were performed by personnel not involved in any aspect of the randomization process. Only the data managers, study statisticians, and the data monitoring committee saw unblinded data, but none of them had any contact with study participants. Blinded tapering was accomplished by dovetailing the induction- and maintenance-phase medication. The induction dosage was reduced whereas the maintenance dosage was increased such that the total number of tablets taken each day was fixed at the final dosage used to achieve recovery. The duration of the transition varied according to the dosage (number of tablets) received during the induction phase but typically occurred in 14 or fewer days. Patients were evaluated in the office on a monthly basis and via telephone interview at the 2-week point (midpoint) between each visit. The BDI was completed at all of the contact points. Monitoring of depression symptoms at this frequency permitted rapid detection of recurrences. Threshold scores for suspecting depression were based on previous research in patients with diabetes; BDI scores of 10 or greater and 16 or greater have positive predictive values of 0.45 and 0.71, respectively, for major depression.[26] Two consecutive BDI scores of 10 or greater or a single score of 16 or greater occasioned a diagnostic reevaluation using the psychiatric interview. Recurrence of major de-

pressive episode was defined by *DSM-IV* criteria. Patients were referred out of the study for treatment of recurrences.

OUTCOME MEASURES

Demographic and Diabetes Characteristics

Demographic information was gathered during the eligibility determinations and included age, sex, race, marital status, education, and type of diabetes. Other features of depression and diabetes (type and age at onset of diabetes, method of diabetes treatment, family history of diabetes, family history of depression, number of previous depression episodes, and history of depression treatment) and the presence of diabetes complications (neuropathy, retinopathy, nephropathy, coronary heart disease) were determined from an assessment of current symptoms, a physical examination, objective test results obtained by review of clinical records, and the patient's self-report of prior diagnoses.

Assessment of Depression

Major depressive episode at presentation and recurrence were established with the Depression Interview and Structured Hamilton (DISH) scale.[27] The DISH scale was designed specifically to diagnose depression in patients who are medically ill and has been validated for this purpose.[27] Study personnel performing DISH scale interviews were trained by the instrument's developers and the staff of the St Louis site of the Enhancing Recovery in Coronary Heart Disease study,[28] a multicenter clinical trial of treatment for depression after acute myocardial infarction. The severity of depression symptoms was measured using the 21-item BDI and the 17-item HDRS, the latter being embedded in the DISH scale. The BDI requires a patient self-rating from 0 to 3 on 21 items; the HDRS uses a clinician rating from 0 to 3 on 17 items assessed by semistructured interview of the patient. A cumulative total from the addition of individual symptom scores is recorded for each measure. The BDI and the HDRS have been studied extensively and shown to be reliable, valid, and sensitive to change.[29-33] The DISH scale was also used to gather depression history information, including the age at onset, number of prior episodes, duration of the longest episode, and the type and duration of prior treatment. All of the clinician-based assessments, including the DISH scale and HDRS evaluations, were performed by individuals blinded to treatment assignment.

Assessment of Glycemic Control

Glycosylated hemoglobin (HbA_{1c}) levels were measured at 2-month intervals up to the time of study completion or depression recurrence to assess glycemic control. The HbA_{1c} level measurement is an aggregate measure of glycemic control over the 120-day period before testing.[34,35] Because of the time interval incorporated in a single HbA_{1c} measurement and the short interval between depression assessments, all of the values obtained following randomization were considered reflective of the depression-free interval following recovery.[2] The HbA_{1c} level was determined using a Bayer DCA 2000 glucometer (Bayer HealthCare LLC, Tarrytown, NY), a model certified for its comparability to the reference methods established by the Diabetes Control and Complications Trial.[36]

A PRIORI SAMPLE SIZE ESTIMATES

A number of assumptions were made in estimating the sample size that would be needed to test the primary hypothesis. One-year recurrence rates were estimated at 80% for the placebo group based on natural observation data in diabetic samples[10] and 40% in the active treatment group from available observations of maintenance management in patients with depression but not diabetes.[37] Given these assumptions, a 2-tailed test of significance based on power of 0.80 and $P<.05$ required that 125 subjects complete the maintenance phase of the study. The rate of subject attrition during the maintenance phase of treatment was expected to be approximately 20% based on follow-up observations of patients with both diabetes and depression who received treatment.[7,38] Thus, for 125 patients to complete the maintenance phase of treatment, approximately 156 patients with depression would have to complete the induction phase of the study and be randomized to maintenance therapy. For 156 patients with depression to complete the induction phase, 262 patients with depression would have to be enrolled and begin receiving induction treatment. (This assumes a 15% dropout rate during open-label treatment and a 70% rate of depression remission.[39,40])

STATISTICAL ANALYSIS

Differences in the demographic and clinical characteristics of subjects randomized to sertraline or placebo were determined in the intention-to-treat samples using the Fisher exact test for categorical data and the *t* test for continuous data. The primary analysis was a between-group comparison of the time to recurrence of major depression. The Kaplan-Meier method was used to estimate the survivor functions, and the nonparametric log-rank test was used to test the principal study hypothesis that the recurrence-free interval was significantly longer in patients receiving sertraline than in those receiving placebo. Patients who did not complete the protocol were censored at their time of discontinuation. The elapsed times to recurrence in one third and one half of the patients were extracted from the survival data for descriptive purposes, but these values were not used in subsequent statistical analyses. The Cox proportional hazards regression model was used to calculate the overall effect of treatment in light of baseline differences between treatment groups, and it was also used in secondary analyses to determine whether factors other than treatment effect were responsible for depression recurrence. Two sets of variables were included in the regression: the first comprised predictors of depression recurrence in psychiatric samples, and the second consisted of aspects of diabetes that may predispose patients to recurrent depression episodes.[10,41-43] All of the predictor variables were included without stepwise elimination, and $P<.05$ was required for a significant independent contribution. To explore the effect of treatment on glycemic control, mean values of HbA_{1c} levels were compared at baseline (ie, immediately prior to the start of open treatment) and following depression recovery (induction phase) by using a paired *t* test. An average of the HbA_{1c} levels beyond the randomization value was computed for each subject over the depression-free interval during maintenance therapy. The BDI scores were computed and compared in the same fashion, with the exception that the recurrence value was not used in calculating the mean BDI score over the depression-free interval. Analyses of covariance were used to determine differences between treatment groups in HbA_{1c} levels during the depression-free maintenance interval using baseline and recovery values as covariates.

RESULTS

OUTCOME FROM RECOVERY INDUCTION

Three hundred fifty-one patients with diabetes (mean age, 50.8 years; 60.1% female; 79.5% white; 83.5% with type

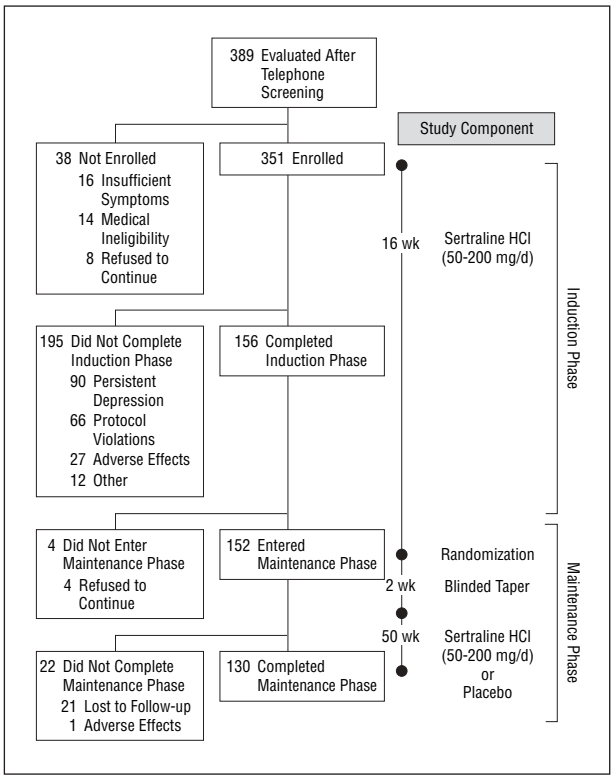

Figure 1. Subject participation in relation to phases of the study design. HCl indicates hydrochloride.

Table 1. Demographics of the Sample in Relation to the Maintenance Treatment Group

Demographic	All Patients (N = 152)	Patients Treated With Sertraline Hydrochloride (n = 79)	Patients Who Received Placebo (n = 73)
Age, mean ± SD, y*	52.8 ± 12.3	50.5 ± 11.7	55.3 ± 12.5†
Female, No. (%)	91 (59.9)	46 (58.2)	45 (61.6)
White race, No. (%)	123 (80.9)	62 (78.5)	61 (83.6)
Married, No. (%)	91 (59.9)	44 (55.7)	47 (64.4)
Education, mean ± SD, y*	14.1 ± 2.6	14.2 ± 2.7	14.1 ± 2.6
Type 2 diabetes, No. (%)	126 (82.9)	64 (81.0)	62 (84.9)

*Grouped data.
†$P<.05$.

2 diabetes) with moderately severe and recurrent *DSM-IV*–defined major depression (mean BDI score, 24.2; mean HDRS score, 17.4; mean number of previous episodes of major depression, 4.9 episodes) received open-label treatment with sertraline during the induction phase of the trial (**Figure 1**). One hundred fifty-six (44%) of these patients satisfied criteria for recovery from the index episode. There were no baseline differences in demographic or depression characteristics between the subsets that did or did not recover. Four patients who recovered withdrew informed consent prior to randomization. The BDI and HDRS scores in the recovered subset decreased by a mean ± SD of 17.7 ± 7.2 and 12.1 ± 4.7 points, respectively ($P \leq .001$ compared with baseline scores). The final score on these measures represented a reduction greater than 50% from the initial scores in 96% (per the BDI score) and 89% (per the HDRS score) of the recovered patients. The mean ± SD sertraline dose required to induce recovery was 117.9 ± 52.1 mg/d. Twenty-seven patients withdrew from the study during induction because of medication adverse effects. Diarrhea was the most frequent adverse effect, and it occurred in 11 (41%) of the 27 patients. The next most common adverse effect was interference with sexual functioning, which occurred in 3 (11%) of the 27 patients. Five serious adverse events were reported; only 1 event (development of psychosis) was judged by us as possibly being related to the medication.

EFFECT OF MAINTENANCE SERTRALINE ON DEPRESSION RECURRENCE

Patients who recovered from depression and continued to the maintenance phase (n = 152) were randomly assigned to double-blind treatment with sertraline (n = 79) or with an identical-appearing placebo (n = 73). The demographic characteristics of these groups at baseline are shown in **Table 1**. There were no significant differences between groups in any of these characteristics except age, with the group receiving placebo being older ($P<.05$). No significant differences were detected between groups in characteristics of depression and diabetes listed in **Table 2**, with the exception that the mean BDI score was slightly lower in the placebo group at the time of randomization to maintenance therapy ($P=.04$). The mean HDRS score at this point was not different between groups ($P=.20$). Of the 152 patients randomized to maintenance, 22 (14.5%) did not complete the protocol. There were no demographic differences between the group that completed the maintenance protocol and those who were lost to follow-up. The likelihood of noncompletion was higher but not statistically different in patients treated with sertraline compared with patients who received placebo (15 [19%] of 79 patients vs 7 [10%] of 73 patients, respectively; $P=.18$). The most common reason for noncompletion was noncompliance with the study protocol (9 [41%] of 22 patients), ie, discontinuing use of study medication (4 [18%] of 22 patients) or failure to return for scheduled follow-up visits (5 [23%] of 22 patients).

Kaplan-Meier estimates of the time to recurrence of depression are shown by treatment group in **Figure 2**. There was a significant difference between groups, with sertraline being more effective in prolonging the depression-free interval (log-rank test, $\chi^2_1=5.4$; $P=.02$), even after controlling for age differences between groups ($P=.01$). The proportional hazard for recurrence on sertraline in this age-controlled model was 0.51 (95% confidence interval, 0.31-0.85). The benefits of sertraline were not diminished when the model was further controlled for the potential but nonsignificant effects of study site ($P=.01$ for sertraline). At 1 year, the calculated rate of nonrecurrence was 65.8% in patients treated with sertraline compared with 47.9% for those who received placebo. Using data available at the 1-year point, the number needed to be treated was 6 patients, ie, it would be necessary to treat 6 patients to spare 1 patient from depression recurrence. Time to recurrence in one third

Table 2. Depression and Diabetes Characteristics of the Sample in Relation to the Maintenance Treatment Group

Characteristic	All Patients (N = 152)	Patients Treated With Sertraline Hydrochloride (n = 79)	Patients Who Received Placebo (n = 73)
Age at depression onset, mean ± SD, y*	32.4 ± 16.2	30.0 ± 14.2	34.9 ± 17.7
Prior episodes of depression, mean ± SD, No.*	4.7 ± 6.3	5.5 ± 8.0	3.9 ± 4.2
Family history of depression, No. (%)†	65 (49.6)	32 (53.3)	33 (46.5)
Prior depression treatment, No. (%)†	79 (56.0)	43 (59.7)	36 (52.2)
BDI score at baseline, mean ± SD*	21.6 ± 6.7	21.7 ± 6.8	21.6 ± 6.6
BDI score at randomization, mean ± SD*	4.0 ± 2.9	4.4 ± 3.0	3.5 ± 2.6‡
HDRS score at baseline, mean ± SD*	15.8 ± 4.4	15.7 ± 4.9	15.9 ± 3.8
HDRS score at randomization, mean ± SD*	3.6 ± 3.1	3.3 ± 2.7	4.0 ± 3.5
Sertraline dose at recovery, mean ± SD, mg/d*	117.9 ± 52.1	119.4 ± 55.5	116.2 ± 48.4
Age at diabetes onset, mean ± SD, y*	43.1 ± 15.8	40.8 ± 14.8	45.7 ± 16.5
Duration of diabetes, mean ± SD, y*	9.7 ± 9.3	9.4 ± 9.3	10.0 ± 9.3
Diabetes complications, No. (%)			
Neuropathy	68 (44.7)	36 (45.6)	32 (43.8)
Nephropathy	16 (10.5)	9 (11.4)	7 (9.6)
Retinopathy	33 (21.7)	19 (24.1)	14 (19.2)
Atherosclerosis	22 (14.5)	11 (13.9)	11 (15.1)
Diabetes management, No. (%)			
Diet only	16 (10.5)	10 (12.7)	6 (8.2)
Insulin	54 (35.5)	28 (35.4)	26 (35.6)
Oral agent	63 (41.4)	32 (40.5)	31 (42.5)
Insulin and oral agent	19 (12.5)	9 (11.4)	10 (13.7)
HbA_{1c} level at baseline, mean ± SD, %*	8.2 ± 1.7	8.2 ± 1.7	8.2 ± 1.7
HbA_{1c} level at randomization, mean ± SD, %*	7.8 ± 1.6	7.9 ± 1.6	7.8 ± 1.6

Abbreviations: BDI, Beck Depression Inventory; HbA_{1c}, glycosylated hemoglobin; HDRS, Hamilton Depression Rating Scale.
*Grouped data.
†Values are provided for those subjects with available data.
‡P = .04 compared with the sertraline group.

of the patients was increased from 57 days in patients who received placebo to 226 days in patients treated with sertraline, and the median time to recurrence was 251 days in the placebo group yet exceeded 365 days (the maximum duration of follow-up) in the sertraline group. Recurrences were not distributed evenly over the 12-month follow-up interval (Figure 2). More than three fourths of the recurrences (in 50 [76.9%] of 65 patients) occurred early, ie, in the first 4 months following randomization. Average BDI scores reflecting specific measurement periods of the study are shown in **Figure 3**.

The Cox proportional hazards model that included well-defined risks for depression recurrence and diabetes characteristics was also used to identify predictors of depression recurrence. Tested risk factors were age, sex, marital status, and BDI total score at baseline and at randomization. Placebo treatment continued to have independent predictive value, as did younger age and higher baseline BDI score. Of the diabetes characteristics tested in the model (type of diabetes, duration of diabetes, baseline HbA_{1c} level), only lower baseline HbA_{1c} level emerged as a significant predictor.

EFFECTS OF IMMEDIATE AND SUSTAINED DEPRESSION RECOVERY ON HbA_{1c}

The HbA_{1c} levels at baseline, randomization, and during the depression-free interval prior to recurrence are shown in **Figure 4** for all of the subjects and for subjects grouped according to treatment received during the maintenance phase. The HbA_{1c} level decreased in the overall subject group during the period of depression recovery in which all of the subjects received open-label treatment with sertraline (mean ± SD HbA_{1c} level reduction, –0.4% ± 1.5%; P = .002). When change in the HbA_{1c} level during induction was compared retrospectively according to the treatment received during maintenance, there was no difference between patients treated with sertraline and those who received placebo (P = .77). The HbA_{1c} levels remained significantly lower than baseline during depression-free maintenance (P = .002) and did not differ between treatment groups when controlling for baseline HbA_{1c} level (P = .90).

COMMENT

Contemporary perspectives of depression are evolving, shaped by new information and widespread familiarity with the illness and its burden.[44-47] Once considered primarily benign and curable with treatment, depression now is understood as debilitating, recurring, and in some instances, refractory.[45,48] There is growing awareness of the importance of depression as a risk factor for medical illness,[49] particularly in patients with diabetes or a diabetic predisposition.[50] For example, depression increases the risk of developing type 2 diabetes,[51,52] accelerates the presentation of coronary heart disease in both type 1 and type 2 diabetes,[3] and significantly increases the risk of diabetes-related mortality.[6,53,54] Time

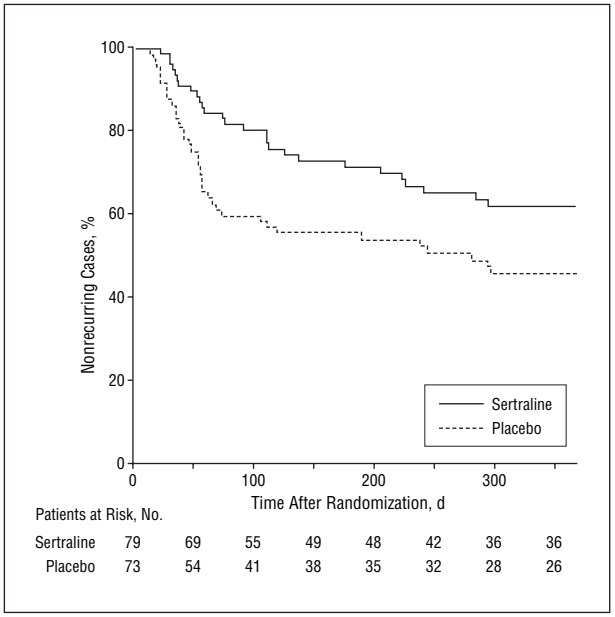

Figure 2. Kaplan-Meier estimates of the time to recurrence of major depression in patients randomized to treatment with sertraline hydrochloride or placebo. The difference between groups was statistically significant (log-rank test, χ^2_1=5.4; *P*=.02), with sertraline prolonging the depression-free interval of maintenance.

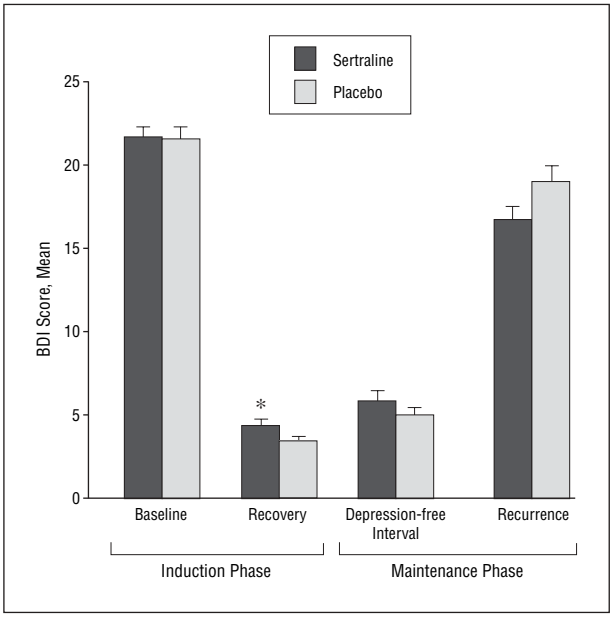

Figure 3. Mean Beck Depression Inventory (BDI) score at time points during induction and maintenance phases of the study. The recurrence BDI score was calculated for the subset of patients who had a recurrence of major depression during the maintenance phase. The BDI scores were slightly higher at recovery in the patients treated with sertraline hydrochloride as compared with patients who received placebo but did not differ between groups at the other time points. Error bars indicate SEM. **P*=.04.

spent depressed (ie, the cumulative chronicity of depression over the patient's lifetime) is suspected of being an important contributor to medical morbidity.[3,55] Since most patients with depression receive no specific antidepressant treatment,[56,57] most episodes (1 episode per year on average) are quite lengthy. In diabetic as well as psychiatric populations, conventional treatments are effective in the short term; unfortunately, treatment is often provided only briefly,[58-60] received at doses that are psychiatrically subtherapeutic,[48,61] or discontinued at or before the point of depression relief.[62-64] Not surprisingly, most patients with diabetes redevelop depression within a year of successful treatment. To our knowledge, whether providing maintenance treatment could alter this recurrence pattern had not been examined prior to this study.

Our study clearly shows the advantage of sertraline over placebo in preventing recurrence of depression in patients with diabetes. The proportional hazard for recurrence was 0.51 (95% confidence interval, 0.31-0.85), suggesting that a patient who received placebo and did not have recurrence at a given point had twice the chance of recurring by the next point in time as compared with a patient treated with sertraline.[65] The time elapsed before one third of the subjects had recurrence was nearly 4 times longer in the sertraline group, with the advantage of treatment being detectable even though the 12-month rate of recurrence in the placebo group was lower than that observed in previous natural history studies of patients with both depression and diabetes.[10,11] Our findings provide further evidence of the prophylactic efficacy of antidepressant pharmacotherapy, extending prior observations made in psychiatric[66-69] and primary care samples[70] to patients with comorbid diabetes.

In the analysis of clinically relevant covariates, higher baseline BDI scores, younger ages, and lower baseline HbA_{1c} levels emerged as significant predictors of recurrence. In our sample, younger patients were those aged approximately 40 to 50 years. Such patients as well as those having more severe depression symptoms at presentation were found to have a higher risk of recurrence in previous studies of patients receiving psychiatric care.[70,71] Residual symptoms at the point of remission or recovery, a robust predictor in these earlier studies,[72,73] were correlated with the baseline BDI score, less predictive of recurrence than baseline depression severity, and not retained in our model. In previous studies,[11,41] we found that higher HbA_{1c} levels predicted a more severe depression course and less responsiveness to initial therapy. The finding that lower HbA_{1c} levels predicted recurrence during maintenance appears at odds with these earlier observations, suggesting that the full relationship of the HbA_{1c} level to outcome of depression management remains to be determined. The weight of the evidence may indicate that risk for recurrence is more strongly predicated on depression and demographic characteristics than on diabetes features. However, other aspects of the HbA_{1c} level, including its seasonal variation,[74] may have influenced the results and require consideration.

Although sertraline conferred protection from recurrence, not all of the treated patients benefited. Only 44% of those who entered open-label treatment with sertraline adhered to treatment, tolerated the medication, and recovered from the index episode of depression. Of those who recovered and were randomized to sertraline maintenance, one third had a recurrence and another one fifth failed to complete the study protocol, the latter rate being higher but not statistically different from that of the placebo group (*P*=.18). Typical of most studies of depression prophylaxis, the majority of recurrences occurred in the 2 months immediately following randomiza-

tion.[67-69,71] Thus, although there was a clear prophylactic effect of sertraline, it surfaced in the context of conspicuous and continuous susceptibility to depression. The cause of this vulnerability remains unclear; medical comorbidity such as diabetes is itself a risk factor for chronic depression.[75] Other potential contributors in this sample include insufficient duration of induction treatment, inadequate taper duration, interruption of a neurochemical homeostasis established with acute-phase therapy, incomplete long-term potency of sertraline, or the pernicious character of depression.

Considering the bounty of similar studies in psychiatric samples reporting high rates of initial treatment discontinuation or rapid recurrence[67,68,76,77] and those finding limited[70] or no[78] effect of antidepressant treatment, pharmacotherapy alone appears unlikely to provide durable relief of depression in the majority of cases—possibly being viewed as a temporizing measure, reigning in depression in the short term and allowing for the introduction of other more effective long-term therapies. Vigilant monitoring of depression symptoms to prompt treatment augmentation or modification is required and may improve the picture. In a recent crossover trial[79] involving subjects without diabetes, nonresponders to nefazodone hydrochloride or the cognitive behavioral analysis system of psychotherapy were switched to the alternate treatment with good results. The intention-to-treat response rate, although higher in those crossed over to the cognitive behavioral analysis system of psychotherapy, was clinically significant in both groups (57% vs 42%, respectively; $P=.03$). There also are indications that specific psychotherapy may promote more durable remissions of depression. In a study by Hollon et al,[80] patients with moderate to severe depression who had responded to cognitive therapy were then withdrawn from treatment and followed up for 12 months. Outcomes were compared with those in patients who had responded to medication and were then randomly assigned to continued medication or placebo withdrawal. The relapse rate in the cognitive therapy group (30.8%) was lower than in the placebo group (70.2%) and similar to that in the group that continued to receive medication (47.2%). To this point, the depression treatment outcome data argue for more inclusive paradigms that invite new approaches and novel combinations.

Glycemic control improved significantly during open-label treatment and depression recovery in our patients. These gains were sustained during the depression-free interval of maintenance and did not differ between treatment groups. Sustained periods of depression recovery with psychotherapy had also been associated with glycemic improvement.[9] Whether improvements in glycemic control can be attributed directly to depression improvement or to some other study-related effect cannot be determined from our investigative design. Had glycemic control been measured beyond the point of recurrence and had other factors that affect glucose levels been systematically monitored or controlled, direct longitudinal relationships of depression improvement to changes in HbA_{1c} levels could have been better established. Sertraline did not interfere conspicuously with glycemic control, a noteworthy observation considering the direct hyperglycemic effect of nortriptyline hydrochloride detected in an earlier acute-phase (8-week) treatment trial.[7] As a class, selective serotonin reuptake inhibitors may have advantages over tricyclic antidepressants by being relatively weight neutral.[81,82]

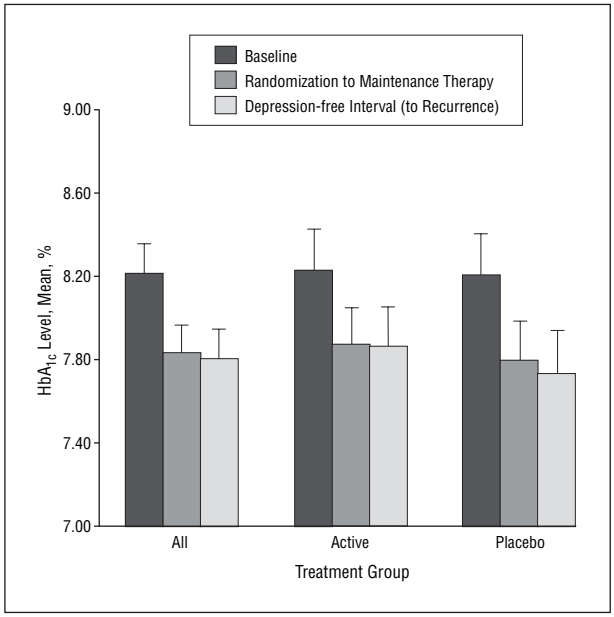

Figure 4. Glycosylated hemoglobin (HbA_{1c}) levels at baseline, randomization, and during the depression-free interval leading up to recurrence (includes all of the postrandomization HbA_{1c} levels). For all of the subjects, open-label treatment with sertraline hydrochloride was associated with a significant decrease in the HbA_{1c} level ($P=.002$). The HbA_{1c} levels during the depression-free period of maintenance therapy leading up to recurrence or until the end of the study were not different for all of the subjects from the level at the time of randomization but remained significantly lower than the baseline levels preceding open-label therapy ($P=.002$). Outcomes were similar for each treatment arm during maintenance, and the HbA_{1c} levels during the depression-free period were similar between the active and placebo groups when controlling for baseline values ($P=.90$). Error bars indicate SEM.

Our study has a number of strengths and some important limitations. To our knowledge, this is the first study of maintenance pharmacotherapy for prevention of depression recurrence in diabetes. Sertraline was selected for study because at the time the study started, it was among the antidepressants most frequently prescribed in primary care settings.[83,84] Its efficacy was determined in rigorous double-blind placebo-controlled fashion that included serial measurements of glycemic control and depression symptoms performed by independent evaluators without knowledge of treatment received. The sample was relatively large (n=152) compared with samples in maintenance studies in psychiatric populations.[68,76,77,79] The survival analysis allowed for the use of data from all of the patients up to the point of a censoring event (premature discontinuation, depression recurrence, or study completion). Weaknesses include failure to measure HbA_{1c} levels beyond the censoring event and other factors (eg, psychiatric comorbidity) that may predispose to depression recurrence.[85] Enrollment resulted in part from advertisement and was predicated on responsiveness to sertraline, limiting the overall generalizability of the findings. The latter mandates a cautionary approach toward interpreting the role of maintenance sertraline in patients who have not dem-

onstrated initial responsiveness. Missing data did not allow for the testing of a more complete set of predictor variables (eg, anxiety symptoms, family history of depression) in the Cox regression model.

Within the limitations outlined, our study establishes a clear benefit of sertraline for prevention of depression recurrence in patients with diabetes. Sertraline lengthened the depression-free interval of maintenance and did not interfere with glycemic improvement achieved during the recovery phase. Treatment with sertraline is relatively simple, safe, and widely available, and although it is not curative, it offers patients with diabetes a potentially viable method for ameliorating the suffering, incapacity, and burden associated with recurrent depression.

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Author Affiliations: Department of Veterans Affairs Medical Center, St Louis, Mo (Dr Lustman); Departments of Psychiatry (Drs Lustman, Clouse, Freedland, Rubin, and Williams and Mr Nix) and Medicine (Drs Clouse, McGill, and Williams), Washington University School of Medicine, St Louis; Department of Psychiatry, University of Arizona School of Medicine, Tucson (Dr Gelenberg); and Departments of Psychiatry and Behavioral Sciences (Dr Ciechanowski) and Medicine (Dr Hirsch), University of Washington, Seattle.
Correspondence: Patrick J. Lustman, PhD, Department of Psychiatry, Washington University School of Medicine, 660 S Euclid Ave, Campus Box 8134, St Louis, MO 63110 (lustmanp@wustl.edu).
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