Fluoxetine for Depression in Diabetes

A randomized double-blind placebo-controlled trial

Patrick J. Lustman, PhD  
Kenneth E. Freedland, PhD  
Linda S. Griffith, MSW  
Ray E. Clouse, MD

OBJECTIVE — Depression is prevalent in patients with diabetes. It is associated with poor glycemic control and is linked to an increased risk for diabetic complications. In this study, we assessed the efficacy of fluoxetine for depression in patients with diabetes.

RESEARCH DESIGN AND METHODS — Sixty patients with diabetes (type 1, n = 26; type 2, n = 34) and major depressive disorder entered an 8-week randomized placebo-controlled double-blind trial. Patients were given daily doses of fluoxetine (up to 40 mg/day). The Beck Depression Inventory (BDI) and Hamilton Rating Scale for Depression (HAM-D) were used to measure the severity of depression and to determine the percentage of patients who achieved substantial improvement or complete remission. GHb levels were obtained to monitor glycemic control.

RESULTS — Reduction in depression symptoms was significantly greater in patients treated with fluoxetine compared with those receiving placebo (BDI, −14.0 vs. −8.8, P = 0.03; HAM-D, −10.7 vs. −5.2, P = 0.01). The percentage of patients achieving a significant improvement in depression per the BDI was also higher in the fluoxetine group (66.7 vs. 37.0%, P = 0.03). Additionally, trends toward a greater rate of depression remission (48.1 vs. 25.9%, P = 0.09 per the HAM-D) and greater reduction in GHb (−0.40 vs. −0.07%, P = 0.13) were observed in the fluoxetine group.

CONCLUSIONS — Fluoxetine effectively reduces the severity of depression in diabetic patients. Our study demonstrated that after only 8 weeks, this treatment also produced a trend toward better glycemic control.

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Major depressive disorder is present in 15–20% of patients with type 1 or type 2 diabetes (1) and has implications that exceed its recognized adverse effects on daily functioning and quality of life (2–4). Depression has been associated with poor compliance with the diabetes regimen (5,6), poor glycemic control (7–15), and an increased risk for micro- and macrovascular complications (16–19). It is not known, however, whether these associations can be altered by the successful treatment of depression.

In general, little is known about the efficacy of antidepressant pharmacotherapy in diabetic patients. Nortriptyline hydrochloride, a secondary amine tricyclic antidepressant, is the only agent previously tested in a placebo-controlled trial with diabetic patients (20). Reduction in depression symptoms was significantly greater in patients treated with nortriptyline compared with those receiving placebo, but the drug had significant adverse effects on glycemic control. Path analysis, controlling for opposing effects, showed that improvement in depression had a clinically significant benefit on glycemic control: depression remission was associated with a 0.8–1.2% reduction in glycated hemoglobin over the 8-week study period (20,21).

Hyperglycemia has not been reported in patients treated with newer classes of antidepressant agents such as the selective serotonin reuptake inhibitors (SSRIs) (22,23). The efficacy of fluoxetine hydrochloride, the first SSRI available in the U.S., for treating depression in healthy patients has been established in a number of controlled clinical trials (24–26), but its usefulness in diabetic patients has been unknown. Tollefson et al. (27) found that fluoxetine was less effective in patients over age 60, which might, the study suggested, partially result from more comorbid medical illness in this age group. The efficacy of depression treatment may be limited by lifestyle restrictions, pain, impairment, and disability—realities that often accompany advancing diabetes (20,21). This study was designed to determine the antidepressant efficacy of fluoxetine in diabetic patients with major depressive disorder. A secondary aim was to study the effects of treatment and depression improvement on glycemic control.

RESEARCH DESIGN AND METHODS

Patients
A study to determine the usefulness of fluoxetine for depression in diabetic patients was reviewed and approved by the Human Studies Committee of Washington University School of Medicine. The study was publicized within the Washington University Medical Center community and through various advertisements in the St. Louis, Missouri, metropolitan area. Patients with type 1 or type 2 diabetes who were 21–65 years of age were eligible to participate, provided they were able to give informed consent and answer questions and fill out research forms on their own. Patients were required to meet diagnostic criteria for a major depressive disorder, a diagnosis that was made with the National Institute of Mental Health Diagnostic Interview Schedule (DIS) (28,29). A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
criteria for major depression and to have a score of $\geq 14$ on either the Beck Depression Inventory (BDI) or the Hamilton Rating Scale for Depression (HAMD). Patients were excluded from participation in the study if they reported active suicidal ideation or a history of attempted suicide; had a history of bipolar disorder or any psychotic disorder; had a current alcohol or other substance abuse disorder; or were currently taking psychoactive medications. Patients for whom fluoxetine therapy was contraindicated were also excluded. This group included patients who were pregnant or lactating, had a history of convulsions or seizure disorder, had clinically significant hepatic dysfunction (liver function tests $>3$ times normal), and renal insufficiency (serum creatinine $>3$ mg/dl).

Assessment of depression

Presence of major Axis I clinical syndromes was determined with the National Institute of Mental Health Diagnostic Interview Schedule (DIS) (28) and diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (29). The reliability and validity of the DIS in psychiatric and epidemiological studies have been extensively reported (30). There is also evidence for the sensitivity and utility of this diagnostic technique in patients with diabetes, in whom some of the somatic symptoms of major depression (such as fatigue, weakness, and sleep and appetite disturbances) may be manifestations of diabetes (31,32).

The severity of the current depression symptoms was measured by the BDI (33) and the HAMD (34). The BDI is both a reliable and valid measure of the severity of depression (35). It requires a self-rating from 0 to 3 on each of 21 items; a cumulative total from the addition of individual symptom scores is recorded. Depression presents similarly on the BDI in diabetic and psychiatric patients (32). The 17-item HAMD is a clinician-rated measure of the severity of depression and has been the primary outcome measure in the majority of studies of antidepressant pharmacotherapy. There is evidence that the HAMD is a valid (36-38) and modestly reliable (39) measure of depression severity.

Assessment of diabetes

GHb levels were measured to assess glycemic control. The GHb level correlates with the average blood glucose concentration over time because the proportion of GHb is a function of the glucose concentration to which the erythrocytes are exposed. The half-life of the erythrocytes is approximately 120 days; hence, GHb therefore reflects the average level of glycemic control during that period (40,41). Whole-blood GHb concentrations were determined using cation exchange column-based high-performance liquid chromatography on the Bio-Rad Variant analyzer (Bio-Rad Laboratories, Hercules, CA) (42). The range of GHb levels for normal nonobese persons in the Barnes-Jewish Hospital outpatient laboratory is 4.0-6.0%. The presence of complications of diabetes (neuropathy, retinopathy, and nephropathy) was determined by the physician-investigator (R.E.C.) on the basis of review of each patient's medical history, current symptoms, physical examination findings, and objective test data (which were obtained through review of clinical records).

Study design

Patients who gave informed consent and met inclusion criteria were randomly assigned to receive fluoxetine or placebo administered in identical-appearing opaque capsules. A computer algorithm determined the randomization pattern. The 8-week treatment period began with the baseline visit and included subsequent visits at the end of treatment weeks 3, 5, and 8. Fluoxetine dosing began at 20 mg a day in the morning and could be increased to a maximum of 40 mg daily in the morning dependent upon side effects and clinical response. Study outcomes were assessed at baseline and at the conclusion of the 8-week treatment period. At each evaluation, assessments of depression and glycemic control were made and scored independently of one another. The study personnel who monitored patient progress were not involved in treatment, and assessors were blinded to treatment assignments. Three patients were permitted to continue amitriptyline for neuropathic pain (25-50 mg/day); otherwise, patients were not allowed to take other psychoactive medications during protocol treatment.

Study personnel did not provide diabetes treatment, and patients continued to see their diabetologists as scheduled or as needed during the trial. At each study visit, patients were asked to describe any major changes in diabetes treatment, and alterations were recorded. At the end of the 8-week trial, any patient who was classified as not depressed (BDI score $\leq 9$) was referred to his or her primary care physician for follow-up, and a letter was sent to the physician summarizing the patient's progress during study treatment. Placebo-treated patients who remained depressed (BDI score $\geq 10$) were given open-label treatment with the active agent (fluoxetine) for 1 additional month. The fluoxetine-treated patients who remained depressed at study's end were referred for further treatment to either their primary care physician (for antidepressant medication) or a psychotherapist.

Statistical analyses

Differences in the demographic and clinical characteristics of subjects receiving fluoxetine or placebo were determined using Fisher's exact test for categorical data and the Student's $t$ test for continuous data. The results of an intention-to-treat analysis of the depression outcomes are provided for the purpose of comparison to other studies (43,44). The primary analyses of study outcomes focused on the "completer" sample. Analyses of covariance (ANCOVAs) were used to determine the effects of treatment on depression (per BDI and the HAMD) and glycemic control (per GHb), with mean baseline scores on these measures used as the covariates. The chi and Fisher's exact tests were used to examine differences in the percentages of patients in each study group achieving significant improvement in depression (posttreatment BDI and HAMD scores $\leq 50\%$ of the pretreatment scores [45]) and depression remission (posttreatment BDI score $\leq 9$ [35], HAMD score $\leq 7$ [46]). Continuous variables are reported as the means $\pm SD$ unless otherwise stated.

RESULTS

Demographic and clinical characteristics

A total of 65 patients gave informed consent to participate and were evaluated to assess their eligibility. Five (7.7%) of these patients were excluded from participation, and 60 (92.3%) met all inclusion criteria and were randomly assigned to 1 of the 2 study groups. Of the 5 excluded patients, 1 (20%) had an exclusionary psychiatric condition, and 4 (80%) were unwilling to take medication. Of the 60 patients who were randomly assigned to treatment, 54 (90%) completed the 8 weeks of treatment and 6 (10%) discontinued participation prematurely. Of the 6 who did not complete the study, 3 (50%) were in the fluoxetine group and 3 (50%)...
Fluoxetine in diabetes

were in the placebo group. Of the 3 noncompleters in the fluoxetine group, 1 was discontinued because of medication side effects, and the remaining 2 withdrew without explanation. Of the 3 noncompleters in the placebo group, 1 was discontinued because of a cardiac event, and 2 withdrew without explanation. There were no significant differences between noncompleters and completers on any of the measured demographic and clinical characteristics: age, race, sex, marital status, education, monthly income, type of diabetes, duration of diabetes, mode of diabetes treatment, prevalence of diabetes complications (neuropathy, nephropathy, retinopathy), or pretreatment GHb and depression levels. There was no evidence of differential attrition. There were no significant differences between the fluoxetine and placebo groups on the report of any of 14 potential side effects. Only 2 side effects (nausea and appetite loss) were reported by 10% of the subjects taking fluoxetine.

Selected demographic, depression, and diabetes characteristics of the 54 patients who completed treatment are shown in Table 1. No statistically significant differences were seen between the study groups in age, race, sex, education, marital status, type of diabetes, duration of diabetes, pre-treatment GHb level, number of previous episodes of depression, and pretreatment scores on the BDI and the HAMD.

Effect of treatment on depression

The effect of treatment on depression symptoms was studied using ANCOVA of posttreatment scores on the BDI and the HAMD, using pretreatment values as the covariate. The results of these comparisons are shown in Fig. 1. Mean posttreatment scores on the BDI and the HAMD were significantly lower in the fluoxetine group compared with the placebo group (BDI, 9.6 ± 8.5 vs. 13.6 ± 10.7, \( P = 0.03 \); HAMD, 9.4 ± 9.1 vs. 14.3 ± 10.6, \( P = 0.01 \)). Reduction in depression symptoms was significantly greater in patients treated with fluoxetine compared with those receiving placebo, whether measured with the BDI (−14.0 vs. −8.8, \( P = 0.03 \)) or the HAMD (−10.7 vs. −5.2, \( P = 0.01 \)).

Depression outcomes were also studied by comparing in the fluoxetine and placebo groups 1) the percentages of patients who achieved a clinically significant improvement in depression (a decrease ≥50% in scores on the BDI and the HAMD) and 2) the number of patients who achieved depression remission (post-treatment BDI score ≤9, posttreatment HAMD score ≤7). The categorical outcomes are summarized in Table 2.

The percentage of patients with significant clinical improvement was significantly greater in the fluoxetine group than in the placebo group when improvement was measured with the BDI (66.7% [18/27] vs. 37.0% [10/27], \( P = 0.03 \)). The fluoxetine and placebo groups were not statistically different when improvement was measured with the HAMD (59.3% [16/27] vs. 40.7% [11/27], \( P = 0.17 \)). A posttreatment BDI score ≤9 was observed in 59.3% (16/27) of the fluoxetine group compared with 40.7% (11/27) of the placebo-treated patients (\( P = 0.01 \)).

Table 1—Selected characteristics of the study sample

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fluoxetine</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>n</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45 ± 13.0</td>
<td>47.7 ± 11.5</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>25 (92.6)</td>
<td>24 (88.9)</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>2 (7.4)</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Female sex</td>
<td>22 (81.5)</td>
<td>16 (59.3)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>19 (70.4)</td>
<td>17 (63.0)</td>
</tr>
<tr>
<td>Not married</td>
<td>8 (29.6)</td>
<td>10 (37.0)</td>
</tr>
<tr>
<td>Level of education (years)</td>
<td>14.3 ± 2.0</td>
<td>13.4 ± 2.2</td>
</tr>
<tr>
<td>Type of diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>13 (48.2)</td>
<td>11 (40.7)</td>
</tr>
<tr>
<td>Type 2</td>
<td>14 (51.8)</td>
<td>16 (59.3)</td>
</tr>
<tr>
<td>Insulin treatment</td>
<td>20 (74.1)</td>
<td>21 (77.8)</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>12.2 ± 7.1</td>
<td>14.1 ± 12.2</td>
</tr>
<tr>
<td>GHb level (%)</td>
<td>8.4 ± 1.7</td>
<td>8.6 ± 1.6</td>
</tr>
<tr>
<td>Weight (lb)</td>
<td>191.2 ± 67.2</td>
<td>207.6 ± 60.1</td>
</tr>
<tr>
<td>Complications of diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathy</td>
<td>17 (63.0)</td>
<td>17 (63.0)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>2 (7.4)</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>9 (33.3)</td>
<td>7 (25.9)</td>
</tr>
<tr>
<td>Previous episodes of major depression</td>
<td>9.4 ± 8.4</td>
<td>7.3 ± 7.4</td>
</tr>
<tr>
<td>BDI score</td>
<td>23.6 ± 8.2</td>
<td>22.4 ± 9.1</td>
</tr>
<tr>
<td>HAMD score</td>
<td>20.1 ± 5.6</td>
<td>19.5 ± 6.9</td>
</tr>
</tbody>
</table>

Data are n, means ± SD, or n (%).
The primary diabetes management regimen of 3 patients (2 in the placebo group, 1 in the fluoxetine group) was changed from oral agents to insulin during the course of the trial. GHb values for these patients were not included in the statistical analysis. Over the course of the trial, improvement in mean GHb level was greater in the fluoxetine group than in the placebo group, but the difference was not statistically significant (−0.40 vs. −0.07%, \( P = 0.13 \)). This statistical trend could not be attributed to differential effects of treatment on weight or on the severity of depression symptoms. ANCOVA was used to test the effect of treatment (fluoxetine vs. placebo) on posttreatment weight, with weight at baseline used as the covariate in the analysis. The analysis showed that treatment had no effect on weight (fluoxetine vs. placebo: least squares means, 204.6 vs. 200.9 lbs, \( P = 0.62 \)). An analysis of responders compared with nonresponders was used to estimate the association of change in depression with change in glycemic control. Responders (n = 26) and nonresponders (n = 25) were defined according to their posttreatment scores on the BDI \( (\leq 9 \text{ vs. } >9) \) or HAMD \( (\leq 7 \text{ vs. } >7) \). There were no significant differences in posttreatment GHb levels of responders compared with nonresponders; whether the threshold score for remission of depression was defined with the BDI (8.3 vs. 8.2%, \( P = 0.9 \)) or with the HAMD (8.4 vs. 8.1%, \( P = 0.6 \)). Finally, patients were grouped according to whether glycemic control improved (posttreatment GHb level - baseline GHb level <0) or did not improve (difference in GHb level =0) during the 8-week trial. The 2 groups were not significantly different on any of the characteristics reported in Table 1. There were statistical trends suggesting that patients whose glycemic control improved were more likely to be younger (\( P = 0.07 \)) and to have type 1 diabetes (\( P = 0.10 \)).

**CONCLUSIONS**—Our findings indicate that fluoxetine is superior to placebo in the management of major depression in patients with comorbid diabetes. The medication was well tolerated, and the rate of study noncompletion was low (10%) and unrelated to fluoxetine treatment. Change in the severity of depression symptoms, whether measured by the BDI or the HAMD, was significantly greater in patients treated with fluoxetine than it was in the placebo-treated control subjects. The percentage of patients whose depression significantly improved was also higher in the fluoxetine group. Although the percentage of patients achieving full syndromal remission did not reach statistical significance over the 8 weeks of the study, a trend in this direction was observed. Response rates might have been higher if the treatment interval had been longer, as is customary in clinical settings.

In patients who completed the trial, the average rate of response ([BDI improved + BDI remitted + HAMD improved + HAMD remitted]/4) was 58.4% in the fluoxetine group compared with 36.1% in the placebo group, a difference of 22.3%. This result compares favorably with the average difference in response, 18.4%, reported by Frank et al. (43) in a meta-analysis of 17 placebo-controlled trials of fluoxetine in medically well psychiatric samples. Nevertheless, although our findings demonstrate the superiority of fluoxetine compared with placebo, they also show that many patients were insufficiently relieved by a relatively short treatment course. Significant residual symptoms (indicated by a BDI score ≥10) were evident in roughly 42% of the patients who received fluoxetine. Of the 16 patients who achieved depression remission, 4 (25%) had a final BDI score ≥7. Scores of this magnitude have been associated with increased risk of recurrence of depression in samples of depressed patients with (47) and without (48) comorbid medical illness. Although clearly not a perfect treatment, the 22.3% increased likelihood of achieving depression remission makes fluoxetine an attractive option for managing depression in diabetes.

The trend toward greater improvement in glycemic control with fluoxetine could not be attributed to differential effects of treatment on weight or depression. It is

<table>
<thead>
<tr>
<th>Table 2—Response to fluoxetine and placebo in the study sample</th>
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<tbody>
<tr>
<td>Intention-to-treat sample (n = 30/group)</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Improved</td>
</tr>
<tr>
<td>BDI</td>
</tr>
<tr>
<td>HAMD</td>
</tr>
<tr>
<td>Remitted</td>
</tr>
<tr>
<td>BDI</td>
</tr>
<tr>
<td>HAMD</td>
</tr>
<tr>
<td>Completer sample (n = 27/group)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Improved</td>
</tr>
<tr>
<td>BDI</td>
</tr>
<tr>
<td>HAMD</td>
</tr>
<tr>
<td>Remitted</td>
</tr>
<tr>
<td>BDI</td>
</tr>
<tr>
<td>HAMD</td>
</tr>
</tbody>
</table>

Data are %. Remitted = posttreatment BDI score ≤9, posttreatment HAMD score ≤7; improved = posttreatment score on the measure is ≥50% of the baseline score.
possible that fluoxetine affected other unmeasured characteristics, such as insulin action, that are important to glycemic control. In obese patients with type 2 diabetes, fluoxetine produced moderate improvements in glycemic control and significant decreases in required insulin levels (23,49,50). Using glucose clamp techniques, Potter van Loon et al. (22) conducted a double-blind placebo-controlled crossover study of 8 obese patients with type 2 diabetes and 8 obese non-diabetic patients after 14 days of treatment with 60 mg of fluoxetine a day. Independent of its effect on weight, fluoxetine improved peripheral and hepatic insulin action. The use of fluoxetine in diabetes may have more than just depression-related effects.

In a controlled trial of cognitive behavior therapy (51), treatment-related improvements in depression produced significant improvements in glycemic control. The effect was most prominent over the 6-month follow-up period. That depression improvement was not significantly related to glycemic improvement in the present study may be due to the short (8-week) period of observation. GHb is a "weighted" measure of mean blood glucose over the preceding 120-day period (40,52), and the posttreatment GHb level, taken on day 56 of fluoxetine treatment, would reflect points in time when the patient was depressed and not yet taking fluoxetine. Consequently, future studies of depression treatment in diabetic patients probably should include systematic observations of GHb for at least 120 days past the termination of treatment.

In this diabetic sample, fluoxetine was a safe and effective therapeutic agent for symptoms of major depression. It was not, however, completely effective in a substantial minority of the cases. Thus, response should be carefully monitored and treatment modified as needed. There was a statistical trend toward a hypoglycemic effect of fluoxetine, suggesting that this agent may have additional positive effects in patients with diabetes. The generalizability of these findings is uncertain; the number of patients completing treatment was relatively small (n = 54), and the patients were not followed beyond the 8-week period of study treatment. The results are nevertheless promising. A trial that includes a longer period of follow-up is needed to determine whether treatment-related improvements in depression lead to sustained improvements in glycemic control. Studies of this type will clarify the full utility of antidepressant therapy in the management of patients with diabetes.

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