Factors Influencing Glycemic Control in Type 2 Diabetes During Acute- and Maintenance-Phase Treatment of Major Depressive Disorder With Bupropion

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OBJECTIVE — Depression management in both short- and longer-term treatment studies has been associated with improvement in glycemic control. We used bupropion hydrochloride (Wellbutrin XL) to determine whether this improvement could be attributed to changes in anthropometrics or diabetes self-care.

RESEARCH DESIGN AND METHODS — Ninety-three patients with type 2 diabetes and major depressive disorder (MDD) received bupropion hydrochloride in a two-phase, open-label treatment trial. Those who completed the acute phase (10 weeks; $n = 75$) and whose depression remitted ($n = 63$) continued bupropion at the remission dose and were followed in the maintenance phase (24 weeks) until attrition ($n = 8$) or relapse of MDD ($n = 0$). Self-report scales were used to measure depression symptom severity and diabetes self-care behaviors. Body composition and glycemic control were determined using dual-energy X-ray absorptiometry and serial determinations of A1C.

RESULTS — BMI, total fat mass, and A1C decreased and composite diabetes self-care improved over the acute phase (-0.5 kg/m^2, -0.7 kg, -0.5%, and $+0.4$, respectively, $P < 0.01$ for each), effects that persisted through the maintenance phase for BMI, A1C, and self-care ($P \leq 0.01$ for each). Reductions in BMI ($B = 0.30$, $P = 0.01$) and depression severity ($B = 0.04$, $P = 0.046$) independently predicted lower A1C after acute-phase treatment, whereas only reduction in depression severity ($B = 0.08$, $P = 0.001$) predicted A1C over the maintenance interval.

CONCLUSIONS — In the short term, improvement in glycemic control during bupropion treatment is predicted independently by improvements in mood and body composition. Longer-term improvements in glycemic control are predicted primarily by sustained improvement in mood via mechanisms independent of anthropometric and self-care modifications.

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Findings from prospective population studies in the U.S. (1–3), Japan (4), Canada (5), and the Netherlands (6) indicate that depression is an independent risk factor for the development of type 2 diabetes. In patients with established diabetes, depression portends a more severe illness course, increasing the risks of micro- and macrovascular disease complications (7). The psychiatric disorder appears to make a causal contribution, at least in some instances. For example, in a 10-year prospective study of women participating in a university hospital–based diabetes registry, Clouse et al. (8) found that major depressive disorder (MDD) identified at the index evaluation predicted the development of clinically evident coronary heart disease, with the effect being independent of traditional risk factors such as smoking, hypertension, and hyperlipidemia.

Depression-associated glucose dysregulation probably contributes to some of these observations. Linkage of depression with hyperglycemia and insulin resistance has been reported in cross-sectional (9–11) and prospective studies (12) and corroborated in meta-analysis (13). In controlled clinical trials, cognitive behavior therapy and conventional pharmacotherapy have proven effective for acute- and maintenance-phase management of MDD in diabetic patients (14–17). Improvement in mood also produced improvement in glycemic control and insulin sensitivity in most (14–18), but not all (19), studies. The effects of antidepressant medication on glycemic control (measured as A1C levels) have been less uniform, with some agents appearing to have direct hyperglycemic effects (e.g., nortriptyline) (15) and others having hypoglycemic effects (e.g., fluoxetine) (16). In other studies, improvements in A1C and/or insulin sensitivity were observed without mechanistic exploration (20). Depression increases the risk of being overweight or obese (21), and antidepressants may independently affect weight and visceral adiposity (5,21). Currently it is not known whether antidepressant treatment–related improvements in A1C are mediated predominantly by weight change, especially during longer-term therapy or through weight-independent effects on factors influencing glucose regulation (e.g., catecholamines, cortisol, and cytokines).

The antidepressant properties of bupropion have been demonstrated in controlled and open-label studies of psychiatric patient samples (22–25),

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Abbreviations: BDI, Beck Depression Inventory; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed.; HDRS, Hamilton Depression Rating Scale; MDD, major depressive disorder; PHQ-9, Patient Health Questionnaire; SDSCA, Summary of Diabetes Self-Care Activities.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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and it has gained favor for having efficacy comparable to that of other antidepressants yet with fewer side effects (22,26,27). Bupropion does not interfere with sexual functioning and has been associated with significantly greater weight loss compared with placebo in randomized, double-blind, placebo-controlled studies of overweight and obese individuals with (28) and without (29) depression. Jain et al. (28) studied 422 obese patients with depressive symptoms who received randomized treatment with bupropion or placebo and were followed for 26 weeks while receiving a 500 kcal/day-deficit diet. The group receiving bupropion lost more weight (4.4 vs. 1.7 kg, $P < 0.001$) and had a higher percentage of patients who lost at least 5% of their baseline weight (40 vs. 16%, $P < 0.05$) than the placebo group. On the basis of these collective observations, we designed a study to see *1*) whether A1C improved during acute- and maintenance-phase treatment with bupropion and *2*) whether changes in A1C were related to changes in mood, diabetes self-care, or anthropometrics. Because we expected to see weight reductions with bupropion, the study might provide strong evidence of weight-independent effects of depression improvement on glycemic control, if they exist.

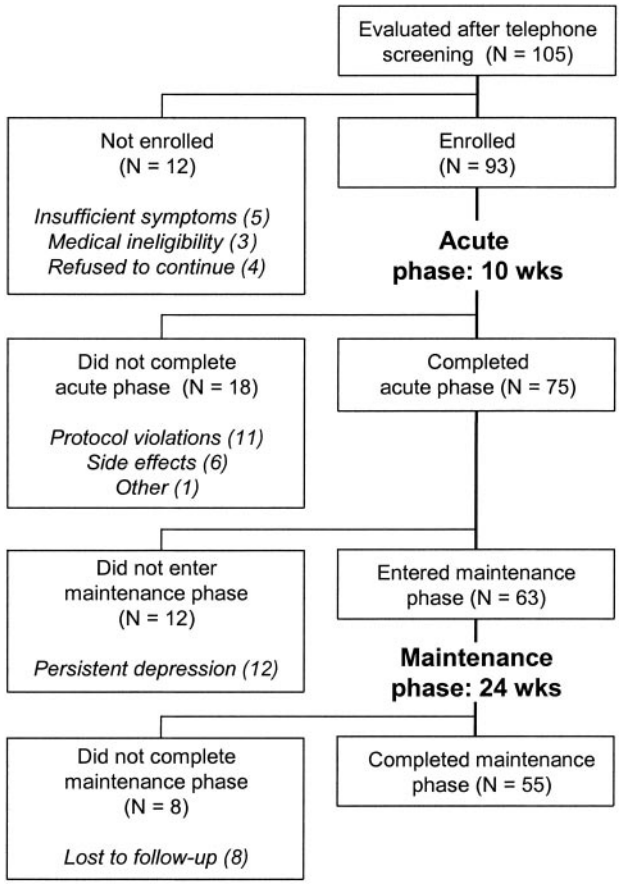

Figure 1—*Subject participation in relation to phases of the study design.*

RESEARCH DESIGN AND METHODS

— The study was a two-phase depression treatment trial. In phase one (acute), patients with MDD received up to 10 weeks of open-label treatment with bupropion. In phase two (maintenance), those who achieved remission of MDD continued to receive bupropion at the remission dose and were followed for up to 24 weeks or until MDD returned. The primary outcome measure was glycemic control, measured with serial determinations of A1C over the 34-week study interval. As the study involved open-label treatment of MDD with bupropion, depression outcomes were considered secondary. Thus, the duration of the acute phase (10 weeks) was constructed to allow sufficient time for an adequate trial of bupropion without compromising the patient's ability to get other treatment in the face of suboptimal improvement. Measures of depression symptom severity, diabetes self-care, BMI (weight in kilograms divided by the square of height in meters), body composition (total body fat and percent body fat), and diabetes self-care behaviors were taken during the acute- and maintenance-treatment phases. We hypothesized that all measures would reflect significant improvement during treatment and that improvement of depression would predict the A1C level after acute-phase treatment and over the depression-free interval of maintenance independent of the effects of other measured factors.

Patients were recruited from January 2004 through November 2005 via advertisements in public media or by referral from university-based diabetes educators and physicians. Study treatment was completed by March 2006. To enroll, patients were required to be 18–80 years of age, have type 2 diabetes, and meet the criteria for MDD as defined in the *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. (DSM-IV) (30). Patients were excluded from participation for having active suicidal ideation, a history of attempted suicide, received electroconvulsive therapy within the 3 months before study entry, a history of psychotic disorder, organic mental disorder, current alcohol or other substance abuse disorder, or a contraindication to bupropion or being unwilling to discontinue other psychoactive medications. Patients with advanced hepatic or renal disease, those with a history of treatment with monamine oxidase inhibitors, or those who had been taking benzodiazepines, terfenadine, astemizole, or digoxin within 3 months of study entry were also excluded, as were those with a history of seizure disorder and women who were pregnant or were lactating. Patients taking an antidepressant at the time of study enrollment were tapered off the medication over an interval ≤2 weeks while bupropion was introduced. Informed consent to participate was obtained from all patients before undergoing medical and psychiatric evaluations. The study was reviewed and approved by the Washington University Medical Center Human Studies Committee. One hundred and five individuals underwent telephone screening and subsequent in-office evaluations. Of these individuals, 93 (90.2%) satisfied all eligibility requirements and were enrolled in the study (Fig. 1).

Bupropion therapy and monitoring

Enrolled subjects began open treatment with 150 mg/day bupropion hydrochloride extended release (Wellbutrin XL) administered in the morning. The dose was adjusted biweekly by increments of 150 mg/day during the acute phase to a maximum of 450 mg/day, depending on side effects and clinical response. The final dose used to achieve recovery during the acute phase was continued during the maintenance phase without adjustment. At each study office visit, the patient was seen by the physician assistant and the psychiatric technician. Psychometric assessments were performed by the technician independent of the physician assistant's assessment. The physician assistant evaluated the clinical response and provided clinical management with the structure of the interaction guided by the manual used in the National Institutes of Mental Health Treatment of Depression Collaborative Research Program (31). Initial treatment sessions lasted 45–60 min, and subsequent sessions lasted 15–30 min. Visit frequency was every 2 weeks during the acute phase and every 8 weeks during maintenance; the latter was designed to resemble a primary care monitoring schedule.

A partial remission was required to continue to the maintenance phase and was defined as the absence of MDD per DSM-IV criteria and a Beck Depression Inventory (BDI) score ≤9 at the 10-week assessment. During maintenance-phase observation, a BDI score ≥14 was considered cause for psychiatric diagnostic reevaluation to determine whether MDD had returned. In depression screening studies of diabetic patients, a BDI total score ≥14 has had positive predictive values of 0.57 and 0.65 for MDD when the base rate of depression is 15 and 20%, respectively (32).

Measures

Demographic and diabetes characteristics. Demographic information including age, sex, race, marital status, education, and type of diabetes was gathered during the eligibility determinations. Other features of depression and diabetes (age of 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, and coronary heart disease) were determined from a composite assessment of current symptoms, physical examination, objective test results obtained by review of clinical records, and patient report of prior diagnoses. Changes in diabetes management regimens were recorded at each visit.

Assessment of depression. The presence of MDD was assessed using the Diagnostic Interview Schedule–Version IV (30), a highly structured psychiatric interview that allows assignment of diagnoses in accordance with the criteria set forth in DSM-IV (33). The severity of current depression symptoms was measured using two self-report measures, the BDI (34) and the Patient Health Questionnaire-9 (PHQ-9) (35), and one clinician-based assessment, the Structured Interview Guide for the Hamilton Depression Rating Scale (HDRS) (36). The BDI has been the measure most frequently used in depression treatment trials in diabetic populations (14–16) and was identified before data collection as the primary measure of depression severity.

Assessment of glycemic control and diabetes self-care behaviors. A1C levels were measured before and after the acute phase and bimonthly during maintenance. A1C is an aggregate measure of glycemic control over the 120-day period before testing (37). Because of the time interval incorporated in a single A1C measurement, the short interval between depression assessments, and the fact that follow-up was scheduled up to the point of relapse or recurrence, all values obtained during the maintenance phase were considered reflective of the depression-free interval after remission (17,38). A1C level was determined using a Bayer DCA2000 glucometer, a model certified for its comparability to the reference methods established by the Diabetes Control and Complication Trial (39).

The Summary of Diabetes Self-Care Activities (SDSCA) (40) scale is a 12-item self-report questionnaire that measures levels of self-care behavior and the degree of adherence with medical provider–recommended activities. Toobert et al. (41) provided a psychometric review attesting to the reliability and validity of the SDSCA scale. In the present study we used the SDSCA questions that assess diet amount, exercise, and adherence to glucose monitoring, domains with potential relevance to depression. Raw score averages were calculated for each of these subscales. These indexes provided a meaningful way of characterizing changes in self-care that occurred during the trial. Higher scores indicate greater attention to self-care. Raw scores for each were converted to *z* scores and also were averaged to form an aggregated *z* score for the SDSCA.

Anthropometrics and body composition analyses. At each study visit, height was measured to the nearest 0.5 cm with the patient in bare feet, and weight was measured on a balance scale to the nearest 0.5 kg. BMI was calculated by dividing body weight (in kilograms) by the square of height (in meters). Total body fat mass and percent body fat were determined by using whole-body dual-energy X-ray absorptiometry (QDR-1000/W; Hologic, Waltham, MA) according to a previously described validated method (42). Body composition was measured at baseline, after acute-phase treatment, and at the final maintenance visit.

Statistical analysis

Measures of central tendency were reported as means ± SD for continuous variables unless otherwise noted. Mean A1C values before and after acute-phase treatment were compared using a paired Student's *t* test. An average of the A1C levels beyond the acute phase was calculated for each subject over the depression-free interval of maintenance. Values for the BDI, BMI, total body fat mass, percent body fat, and SDSCA scales were computed and compared in the same fashion with the exception that total body fat mass and percent body fat were measured only at the primary observation points: pretreatment, after acute-phase treatment, and at the conclusion of maintenance. All changes were calculated by subtracting the baseline value from the follow-up value for reporting summary changes and for use in subsequent regression models. Changes in diabetes management regimens were coded linearly (decrease, no change, or augmentation) for each study phase. Linear regression on A1C was performed to identify predictors of A1C *1*) after acute-phase treatment and 2) during the depression-free interval of maintenance. Independent variables included in the two regression analyses were changes in BMI, BDI, diabetes management, and SDSCA scale scores from the baseline values. Baseline A1C was also included in the models. Body composition measures were highly correlated with each other and with BMI. Thus, BMI was included in the regression model, whereas body composition variables were used only in ex-

Table 1—*Clinical characteristics of the type 2 diabetic sample*

Characteristic	Subjects starting bupropion	Subjects completing acute bupropion treatment	Subjects not completing acute bupropion treatment
n	93	75	18
Age (years)	51.7 ± 9.0	52.2 ± 8.5	49.7 ± 11.0
White	44 (47.3)	41 (54.7)	3 (16.7)*
Female sex	60 (64.5)	46 (61.3)	14 (77.8)
Married	44 (47.3)	34 (45.3)	10 (55.6)
Education (years)	14.3 ± 2.25	14.5 ± 2.2	13.0 ± 2.3
Age of diabetes onset (years)	44.6 ± 9.7	45.1 ± 9.5	42.3 ± 10.5
Duration of diabetes (years)	7.4 ± 7.8	7.3 ± 7.2	7.9 ± 10.1
Weight (lb)	229.5 ± 49.4	230.7 ± 47.9	224.4 ± 56.3
BMI (kg/m^2)	36.0 ± 7.5	35.8 ± 7.2	37.2 ± 8.8
A1C (%)	8.3 ± 2.0	8.2 ± 2.1	8.6 ± 1.9
BDI total score	23.1 ± 7.2	22.9 ± 7.1	23.9 ± 8.0
Age at MDD onset (years)	28.0 ± 13.7	26.7 ± 12.8	34.1 ± 16.2†

Data are *n* (%) or means ± SD. *$P = 0.007$; †$P = 0.05$.

ploratory analyses of BMI-A1C relationships. Results are presented as standardized (β) and unstandardized (B) regression coefficients with 95% CIs. $P < 0.05$ was used as the determinant of statistical significance for all analyses.

RESULTS — Selected demographic, depression, and diabetes characteristics of the sample are presented in Table 1 for all subjects who entered the trial and for whom bupropion treatment was initiated ($n = 93$) and according to whether they did ($n = 75$) or did not ($n = 18$) complete the acute phase of treatment. Those who failed to complete this phase were significantly more likely to be African American ($P = 0.007$) and older at the first onset of major depression ($P = 0.05$); the groups were otherwise similar statistically on the measured clinical characteristics shown in the table. Six patients (6.5%) withdrew from the study during the acute phase because of medication side effects (Fig. 1). Increased anxiety was the most frequent side effect and occurred in three of the six patients. The next most common side effects were nausea, dizziness, and skin irritation, each occurring in two patients. No serious adverse events were reported. Augmentation of diabetes management occurred in 12 patients during the acute phase and in 2 patients during the maintenance phase. The management regimen was decreased in one patient during the acute phase and in four patients during the maintenance phase.

Effects on mood and diabetes self-care behavior

Of the 75 patients who completed the acute phase, 63 (84%) satisfied the criteria for remission after 10 weeks of treatment. The mean daily dose in those who completed the acute phase was 334 mg/day (median 300 mg/day, range 150–450 mg/day). The average daily dose of bupropion was higher in the subset whose depression failed to remit, as expected, given the protocol increases in bupropion in the case of insufficient response (400 vs. 321.4 mg/day, $P = 0.02$). Severity of depression declined significantly on all measures during the acute phase in the subset whose depression remitted (BDI −18.1 ± 7.1, $P < 0.01$; PHQ-9 −6.8 ± 5.4, $P < 0.01$; HDRS −14.9 ± 5.8, $P < 0.01$). However, in the subset whose depression did not remit, significant improvement was seen on some, but not all, measures (BDI −7.9 ± 10.2, $P = 0.02$; PHQ-9 −5.9 ± 6.4, $P = 0.01$; HDRS −2.67 ± 5.9, $P = 0.14$).

Of the 63 patients whose depression remitted and whose treatment continued beyond the acute phase, 55 (87.3%) completed the subsequent 24 weeks of maintenance and 8 (12.7%) discontinued participation prematurely. These groups did not differ significantly in terms of age, race, sex, or severity of depression symptoms at baseline. All 55 (100%) of those who completed the maintenance phase remained free of MDD throughout this phase. The BDI total score remained ≤9

Table 2—*Changes in anthropometrics during acute and maintenance phases relative to pretreatment baseline values*

Measure	Change from baseline during the acute phase			Change from baseline during the maintenance phase for all subjects†
	All subjects*	MDD remitted	MDD not remitted	
n	75	63	12	55
Weight (kg)	−1.6 ± 3.3 (< 0.0001)	−1.5 ± 3.5 (0.001)	−2.3 ± 2.3 (0.005)	−2.1 ± 4.7 (0.001)
BMI (kg/m^2)	−0.5 ± 1.1 (<0.0001)	−0.5 ± 1.2 (0.002)	−0.7 ± 0.8 (0.01)	−0.7 ± 1.6 (0.002)
Total body fat (kg)	−0.7 ± 1.8 (0.004)	−0.7 ± 1.9 (0.02)	0.9 ± 0.9 (0.02)	−1.4 ± 4.6 (0.06)
Percent body fat (%)	−0.03 ± 1.3 (0.8)	−0.03 ± 1.4 (0.9)	−0.1 ± 0.6 (0.7)	−0.03 ± 2.5 (<0.41)

Data are means ± SD (*P* value). *Does not include 18 subjects who failed to complete the acute phase. †Does not include 8 subjects who failed to complete the maintenance phase.

throughout maintenance in 41 (74.5%) of the 55; this subset thus qualified sequentially for full remission and then recovery from the index episode of MDD (30).

Raw scores on the SDSCA subscales measuring adherence to diet and exercise improved significantly during acute-phase treatment (+0.3 ± 0.8 and +0.7 ± 1.8, respectively, $P = 0.002$ for each comparing baseline to 10-week values) and remained significantly improved during the depression-free interval of maintenance compared with the baseline values (+0.3 ± 0.8 and +0.4 ± 1.5, $P = 0.002$ and 0.02, respectively). Adherence to glucose testing did not change significantly over the course of the study (acute phase +0.3 ± 1.7, $P = 0.23$; maintenance phase −0.1 ± 1.5, $P = 0.71$). The summary scale score improved significantly over the acute phase (+0.4 ± 1.0, $P = 0.001$) and remained improved but not significantly so during the depression-free interval of maintenance (+0.2 ± 1.0, $P = 0.06$).

Effects on body composition

Changes in anthropometrics during the acute and maintenance phases relative to pretreatment baseline values are shown in Table 2. Anthropometric measures except percent fat declined significantly during the acute phase in the 75 patients who completed this phase of treatment. Similar changes were observed within the subsets of patients whose MDD remitted or did not remit during the acute phase. In the 55 patients who completed the maintenance phase, changes from baseline over the maintenance interval were significant for weight and BMI; total body fat mass showed a trend toward significance, and, in this instance, the reduction in percent body fat was also significant.

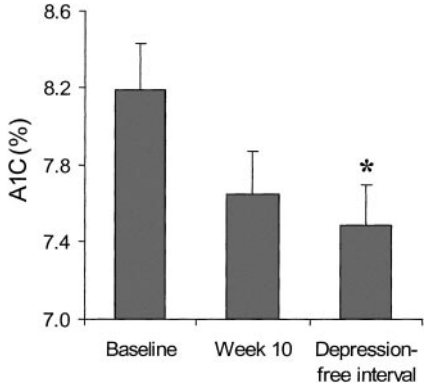

Figure 2—*A1C values at baseline, after 10 weeks of (acute-phase) treatment, and during the subsequent 24 weeks of maintenance treatment. Acute-phase treatment with bupropion was associated with a significant decrease in A1C* (n = *75) that persisted over the maintenance interval* (n = *63). *P < 0.001 compared with baseline.*

Effects on glycemic control

A1C levels at baseline, at the end of the acute-phase treatment, and during the depression-free interval of maintenance are shown in Fig. 2 for all subjects who completed the study. A1C decreased in the overall subject group during the acute phase (−0.5 ±1.0%, $P < 0.001$). The effect was completely attributable to changes in the subset showing remission (−0.6 ± 1.1%, $P < 0.001$), as the change in those who did not show a remission was minimal and insignificant (−0.1 ± 0.7%, $P = 0.7$). A1C levels remained significantly lower than baseline during the depression-free interval of maintenance (−0.7 ± 1.3%, $P < 0.001$).

Predictors of A1C at the conclusion of the acute phase and during the depression-free interval of maintenance were identified in separate multiple regression analyses that controlled for A1C at baseline (Table 3). Changes in BMI, BDI, and subscales of the SDSCA over the acute phase and over the depression-free interval of maintenance were included in the first and second models, respectively. The multiple R, R^2, and F associated with the models were 0.88, 0.78, and 25.3 (model 1) and 0.85, 0.71, and 18.2 (model 2), respectively. Significant predictors in the first analysis (acute phase) were baseline A1C as well as improvement (reduction) in the BDI and BMI. Only baseline A1C and improvement in depression were retained as significant predictors in the second analysis (maintenance phase), with reduction in BMI trending toward significance. The pattern of findings was similar when total body fat mass was substituted for BMI in the regressions, with reduction in total body fat mass predicting A1C for the acute phase ($B = 0.26$, $P = 0.001$) but not for the maintenance phase ($B = 0.13$, $P = 0.16$). Percent body fat was not a significant predictor at either point when substituted for BMI (acute-phase $B = 0.02$, $P = 0.81$; maintenance-phase $B = 0.12$, $P = 0.18$).

CONCLUSIONS — Our study was designed to evaluate the plausibility of some mechanisms that accompany treatment of MDD in patients with diabetes, which were postulated in previous research to account for improvements in A1C (14–16,43). We selected bupropion because it is capable of reducing depression and weight simultaneously and hypothesized that these effects would be accompanied by improved glycemic control in diabetic patients with MDD. This was neither an efficacy nor effectiveness trial but rather an experiment in which bupropion was used to perturb depression and anthropometrics. The relationships of these perturbations to changes in

Table 3—*Predictors of A1C after acute-phase and during maintenance-phase bupropion treatment of MDD*

	After acute phase			During maintenance phase		
Predictor*	β	*B* (95% CI)	*P*	β	*B* (95% CI)	*P*
Change in BDI	0.16	0.04 (0.00 to 0.08)	0.046	0.34	0.08 (0.03 to 0.12)	0.001
Change in BMI	0.19	0.30 (0.07 to 0.53)	0.013	0.12	0.12 (−0.05 to 0.3-)	0.160
Change in SDSCA diet	0.09	0.20 (−0.15 to 0.55)	0.250	0.02	0.04 (−0.33 to 0.40)	0.835
Change in SDSCA exercise	−0.03	−0.03 (−0.18 to 0.11)	0.657	0.03	0.03 (−0.17 to 0.23)	0.761
Change in SDSCA glucose testing	0.05	0.05 (−0.11 to 0.22)	0.511	0.04	0.04 (−0.16 to 0.24)	0.668
Change in diabetes management	−0.01	−0.02 (−0.67 to 0.62)	0.945	−0.06	−0.20 (−0.77 to 0.36)	0.480
Baseline A1C level	0.82	0.71 (0.57 to 0.86)	0.000	0.87	0.68 (0.53 to 0.84)	0.000

*All change scores were calculated by subtracting baseline values from end point values as described under RESEARCH DESIGN AND METHODS.

A1C, when examined within the context of alterations in diabetes self-care that can accompany mood improvement, were then studied over time intervals corresponding to milestones in depression management (i.e., acute- and maintenance-phase treatment). This study had the potential to demonstrate that depression improvement has a favorable effect on glycemic control that is weight independent and unrelated to improved diabetes self-care, a finding that would support the presence of other mediators of the depression-hyperglycemia relationship (13,38).

As we had anticipated, bupropion treatment of our diabetic subjects was accompanied by significant reductions in depression. Depression remitted in 68% of those who started bupropion treatment and in 84% of those who completed the acute phase. Of those whose depression remitted and who continued to receive bupropion, 87% completed the subsequent 6-month study interval, and none of these had a recurrence. Improvements in depression were accompanied by improvements in anthropometrics, some diabetes self-care behaviors, and glycemic control. Reductions in depression severity and BMI each independently predicted lower A1C after the acute phase. Reduction in depression severity was the only independent predictor of A1C over the maintenance interval. The pattern of findings was similar when weight or total body fat was used in place of BMI in the regression model. Whereas SDSCA scale–derived measures of adherence to diet and exercise improved significantly during the acute phase and remained improved during the maintenance phase, these improvements were not independently predictive of improvements in glycemic control over the same intervals.

The findings from the current study replicate those of our previous studies showing that antidepressant pharmacotherapy provides effective relief from depression in diabetic patients and that euthymic effects of depression treatment have euglycemic effects as well (14–17). In the present study, significant improvement in A1C was confined to the subset of patients achieving MDD remission during the acute phase. The unstandardized coefficient for the relationship of depression and A1C was 0.04 for the acute phase and 0.08 for the maintenance phase (Table 3), indicating that for every drop of 1 point in the BDI there were corresponding reductions in A1C of 0.04 and 0.08%, respectively, controlling for other measured factors. Reductions in the BDI in the range of those observed in this study (18.1) could translate to improvements in A1C in the range of 0.6 to 1.2% over intervals corresponding to the acute and maintenance phases. Glycemic control sufficient to avoid complications is difficult to achieve even with intensive diabetes care and monitoring (44). Thus, depression management qualifies as ancillary treatment supporting the end goal of improved diabetes control. Furthermore, to our knowledge, this is the first demonstration of broad improvement in diabetes self-care during depression treatment. In prior studies by Lin et al. (45) and Williams et al. (46), successful depression treatment led to increases in physical activity (46) but had no effect on other aspects of diabetes self-care (e.g., adherence to medical advice regarding diet and glucose testing) (46). The difference may relate to greater improvement in depression symptoms achieved in the present study or the failure of earlier studies to look at an effect of depression improvement independent of treatment.

Finally, we found that depression improvement–related reductions in A1C occurred in the presence and independently of favorable effects on anthropometrics and diabetes self-care. Although weight loss and improved self-care may occur with depression relief, they did not adequately explain the normoglycemic effect of depression improvement. With regard to diabetes self-care, the findings can be compared with those reported in a recent study of patients with type 1 diabetes (38). In that study, depression was associated significantly with higher A1C after controlling for weight and insulin dose, and addition of the SDSCA scale into the mediational analysis had no effect on the parameter estimate, indicating that poor self-care did not mediate the effect.

Although statistically significant, the reductions in weight observed in the subset showing remission over the acute (1.5 kg) and maintenance (2.1 kg) phases were modest. This finding is perhaps disappointing, given the substantial improvement that occurred in mood and the conspicuous linkage of depression with obesity. Simon et al. (21) recently demonstrated that nearly one-quarter of the cases of obesity occurring in the population are attributable to the association of obesity and depression. On the other hand, small durable improvements in BMI are genuine accomplishments and can have significant beneficial effects on health (47). It is encouraging that clinically important improvements in A1C can occur in the absence of large changes in anthropometrics. The findings suggest the possibility of weight-independent physiological mechanisms such as those we postulated previously (38,48). These may include changes to the hypothalamic- and limbic-hypothalamic pituitary-adrenal axes, hippocampal glucocorticoid receptors, the autonomic nervous system, and immunoinflammatory processes (49–56).

Although this study was not a randomized, controlled trial, we were impressed with the high rate of depression remission (87%) and the absence of depression recurrence in those who completed the acute and maintenance phases, respectively. A number of factors may have contributed to these robust benefits in this sample, including open-label administration of treatment, weight loss, the absence of study discontinuation referable to sexual side effects and an overall improvement in sexual functioning in our sample (57), and the more frequent monitoring and greater attention (compared with the general practice setting) that is given to participants in a clinical trial. Given the bidirectional interaction of mood with glucose regulation (48), it is also possible that observed reductions in weight and A1C (and probably insulin sensitivity as well) served to reinforce the antidepressant effects of bupropion or had euthymic effects independent of bupropion. The antidepressant potential of insulin-sensitizing maneuvers, be they behavioral or pharmacotherapeutic, is a matter worthy of future research.

Although this study advances our understanding of the mechanisms involved in the interaction of depression and glucose regulation, it has several important limitations. The fact that bupropion was administered in a research setting and without a comparator treatment limit, respectively, the external and internal validity of the depression treatment findings. The measure of diabetes self-care is not a precise measure of behaviors and may have underestimated the effect. The study was possibly underpowered to detect BMI/total body fat mass effects in the maintenance phase; on the other hand, a larger sample probably would not have diminished the effect of BDI change. The design does not precisely establish the temporal sequences among the vari-

ables; thus, directional statements are meant to be interpreted cautiously. We cannot, for example, rule out the possibility that glycemic improvement preceded and facilitated depression improvement, although the rapid reduction in depression and the aggregate nature of the A1C measure argue against this. With the lack of a placebo-control condition, it is also possible that the improvements in A1C were a direct effect of bupropion, a possibility that merits further study. Despite these evident limitations, our study affirms the importance of depression management in diabetic patients in its potential to improve glycemic control, even though the mechanisms involved are not fully understood. This advantage could lead to better outcomes, measured not only in quality of life but also in reduced or delayed onset of complications.

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