Persistence of Depressive Symptoms in Diabetic Adults

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OBJECTIVE — To determine the level and pattern of persistent depressive symptoms among adults with diabetes and identify factors associated with increased risk of being persistently depressed.

RESEARCH DESIGN AND METHODS — A self-report depression symptom inventory was administered to 245 patients at two initial time points—the beginning and end of a comprehensive outpatient diabetes education program—and at 6-month follow-up.

RESULTS — Only 13% of subjects were persistently depressed (i.e., exceeded the criterion for depression symptoms at all three time points). The rate of being depressed at follow-up was 10% for those negative for depression symptoms at either of the initial time points, 36% for those positive at one initial time point, and 73% for those positive at both initial time points ($P < 0.0001$). Those at increased risk for being persistently depressed were those who did not graduate from high school, had more than two complications of diabetes, and were not treated with insulin.

CONCLUSIONS — Persistent depressive symptomatology is present in a substantial number of diabetic adults and can be effectively predicted using simple screening instruments during initial contacts. Risk factors for being persistently depressed only partly overlap those for transient depressive symptoms and represent a possible biological dimension.

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Previous research has demonstrated that the rate of depression is elevated among diabetic patients relative to the rate in the general population (1). In an earlier study, we found that >40% of diabetic patients had levels of depression symptoms consistent with a psychiatric diagnosis (2). This is consistent with the large body of research on depression in diabetes, which shows high rates in cross-sectional analysis (see references in 1). However, our study identified an unforeseen pattern: among these diabetic patients, all of whom received a psychoeducational intervention incorporating coping skills training (3–5), only 13% remained depressed at three time points over 6 months. This finding inspired the present study.

There has been little longitudinal research on the natural history of depression in diabetes, especially among adults. Existing longitudinal research may have reported overall levels of depression rather than specific rates of transition from depressed to nondepressed conditions and vice versa. Longitudinal research on depression among young type 1 diabetic patients has shown a spike in depression after diagnosis that resolves within a year (6,7). The small amount of research focusing on persistence in diabetic adults has shown that those depressed at an initial screening or diagnosis were likely to experience ongoing depression (8,9). Also little is known about what predicts persistent rather than transient depression. To address these gaps, this study examined the level and pattern of persistent depressive symptoms and the disease and demographic factors associated with being persistently depressed in diabetic patients.

RESEARCH DESIGN AND METHODS

— Our subjects were 245 adults with diabetes who completed a 1-week comprehensive outpatient diabetes education program at the Johns Hopkins Hospital in Baltimore, Maryland; the program has been described in detail elsewhere (2–5). These patients were self-referred or referred by their health care providers in the community and also have been described in detail elsewhere (2). They were included in this study if they filled out symptom inventory questionnaires at the beginning of the program, at the end of the program 5 days later, and 6 months later when patients were contacted by mail. The only difference between those who responded and those who didn't was their marital status (2). Medical and demographic characteristics were obtained by chart review from medical histories performed during program intake (Table 1). HbA_{1c} was measured by gel electrophoresis, with an upper limit for the normal range of the nondiabetic population of 7.7%.

Definition of depression

The self-report questionnaire used to assess depression was the Center for Epidemiological Studies Depression Scale (CESD) (10). The CESD was designed for use in epidemiological population-based studies and contains 20 symptoms, with scores ranging from 0 (rarely) to 3 (most or all of the time), yielding a minimum score of 0 and a maximum score of 60. Items include disturbances of sleep, appetite, and mood and feelings of hopelessness, distractibility, and self-deprecation (but not suicidal ideation or behavior). The symptoms were minimally confounded with symptoms of diabetes; analysis of this confounding showed that it had no effect on the estimated rate of

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Abbreviations: CESD, Center for Epidemiological Studies Depression Scale; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value.

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

Table 1—*Sample characteristics*

Variable	%	Mean ± SD
Age	—	49.8 ± 17.1
Sex (men)	42	—
Race (white and other)	64	—
Married	58	—
Education (high school graduate)	79	—
Duration of diabetes	—	11.9 ± 13.1
HbA_{1c}	—	10.9 ± 2.7
Diabetes		
Type 1	35	—
Type 2 (insulin)	36	—
Type 2 (no insulin)	29	—
Sequelae (>2)	26	—

n = 245.

Table 2—*Pattern of depression symptom persistence*

Total sample	100 (245)							
Preprogram	Positive (+) 38 (93)				Negative (−) 62 (152)			
Postprogram	+ 47 (44)		− 53 (49)		+ 6 (9)		− 94 (143)	
Follow-up	+	−	+	−	+	−	+	−
	73 (32)	27 (12)	37 (18)	63 (31)	33 (3)	67 (6)	10 (15)	90 (128)
% of total	13	5	7	13	1	2	6	52

Data are % (*n*) or %. Percentages are percent of a group from the previous time point who fall into positive and negative subgroups at the current time point, except for total percentages, which are based on the entire sample.

disturbance (2). The specified time period for symptoms was "during the past week." A conventional cutoff point for scores on the CESD depression symptom inventory based on general population samples was chosen as the criterion for disturbance, with a score of ≥16 being considered positive for depression (10). This operational definition does not necessarily correspond to a clinical diagnosis of depression (2).

The persistence of being depressed over the three time points (pre- and postprogram and at 6-month follow-up) was examined. Individuals were considered as being persistently depressed only if they met the criterion for disturbance at all three time points. These data did not allow us to determine whether patients were depressed every week during the 6-month study period. It is not known whether patients received any treatment for depression during the study period.

Analysis

Prognostic statistics (relative risk, sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]) were calculated—alone and in combination—using depression status before and after the inpatient program to predict depression status at follow-up. Sensitivity is the probability of a positive follow-up if the patient had a positive initial result. Specificity is the probability of a negative follow-up if the patient had a negative initial result. PPV is the probability that a positive prediction will be correct; NPV is the probability that a negative prediction will be correct.

To examine the relationship of disease and demographic characteristics to being persistently depressed, logistic regression analysis was performed to estimate odds ratios (OR) and 95% CI. If the 95% CI of a category did not include zero, that category was significantly different from the reference category at the $P < 0.05$ significance level. Factors were entered into the logistic regression model only if they were statistically significant in bivariate analysis. Bivariate analysis used independent sample *t* tests for continuous variables and χ^2 for categorical variables.

RESULTS — As noted in our earlier study (2), only one in eight patients (13%) was positive for depression symptoms at all three time points (Table 2). Participation in the psychoeducational program incorporating coping skills training was associated with a major reduction (53%) in the rate of disturbance among those initially depressed; only a handful (6%) of those not depressed at the outset became depressed during the program.

Those patients depressed before or after the program had a significantly higher risk of depression at 6-month follow-up than patients not depressed at those times (preprogram OR = 8.2, postprogram OR = 9.0; $P < 0.0001$) (Table 3). Preprogram depression had higher sensitivity and NPV; postprogram depression had higher specificity and PPV.

In the multivariate analysis, being depressed at the pre- and postprogram time points each had a significant effect on being depressed at 6-month follow-up (preprogram OR = 5.1, postprogram OR = 4.5; $P < 0.001$). Prognostic statistics showed minor differences using combinations of pre- and postprogram scores to predict state of depression at 6-month follow-up as opposed to single scores. If either the pre- and postprogram score, but not both, was positive, prognostic statistics were similar to using preprogram scores alone. If only those positive at both times were predicted to be positive, specificity and PPV improved, but sensitivity and NPV declined. A three-level risk stratification produced the best classification results for follow-up depression: no positive = 10% rate, OR = 1.0; one positive = 36% rate, OR = 4.8 (95% CI = 2.3–10.4); and two positives = 73% rate, OR = 22.8 (95% CI = 9.8–52.6).

A supplementary analysis (results not shown) was conducted on 155 patients who completed a 12-month follow-up for depression. Patterns of persistence across

Table 3—*Prognostic statistics*

Measure	+ Preprogram	+ Postprogram	Either +	Both +
OR (95% CI)	8.2 (4.5–14.7)	9.0 (5.0–16.3)	9.0 (5.0–16.3)	12.2 (6.8–21.9)
Sensitivity	0.74	0.51	0.78	0.47
Specificity	0.76	0.90	0.72	0.93
PPV	0.54	0.66	0.52	0.73
NPV	0.88	0.83	0.90	0.82

Prognostic statistics represent the use of initial (pre- and postprogram) levels of depression symptoms to predict depression symptom level at 6 month follow-up. The left two columns use positive versus negative symptom levels from a single time point. The right two columns use data from the combined time points: "either +" divides initial levels into those with one or two positive scores versus those with none; "both +" divides initial levels into those with two positive scores versus those with one or none.

three equally spaced time points (preprogram and 6- and 12-month follow-up) were quite similar to those presented in Table 2; none of the estimates of persistence over this longer period fell outside the CI for the shorter time period. The rate of persistent depression was 17% and that of persistent nondepression was 51%. The three-level risk stratification for state of depression at 12-month follow-up using initial and 6-month depression as predictors was no positive = 10% rate, one positive = 34% rate, and two positives = 81% rate. Thus failure of depression symptoms to remit after the 1-week psychoeducational intervention had much the same predictive power over the next 6 months as sustaining a state of depression over the 6-month period immediately after the intervention had for the subsequent 6-month period.

The next analyses examined predictors of being persistently depressed using all factors represented in Table 1. The only demographic factor associated with being persistently depressed in bivariate analysis was lack of a high school education, although African-Americans had a marginally higher rate of persistence depression (P = 0.101). Those patients with more than two complications had a higher rate of being persistently depressed, as did patients taking insulin. In the multivariate analysis, type 2 diabetic patients taking insulin (OR = 0.4, P = 0.060) had marginally lower rates, and those without a high school degree (OR = 2.3, P = 0.051) had marginally higher rates of being persistently depressed (Table 4). Type 1 diabetic patients (OR = 0.3, P = 0.016) had significantly lower rates and those with more complications had significantly higher rates (OR = 2.7, P = 0.017). To compare those with high- and low-risk profiles, we computed synthetic (predicted) probabilities of being persistently depressed (2,11). Patients with the lowest risk profile (type 1 diabetes, high school graduate, fewer complications) had a predicted probability of 4% for being persistently depressed; patients with the highest risk profile (type 2 non-insulin-treated, no high school degree, multiple complications) had a predicted probability of 50% for being persistently depressed. Those with the highest risk profile had a higher predicted risk of being persistently depressed than those who scored as depressed at the initial screening (50 vs. 34%), but not as high as those who scored as depressed at both initial screenings (73%).

Table 4—*Predictors of persistent depression symptoms*

Variable	OR (95% CI)	*P* value
Not high school graduate	2.3 (1.0–5.4)	0.051
Sequelae (>2)	2.7 (1.2–6.2)	0.017
Type 2 (insulin)	0.4 (0.2–1.0)	0.060
Type 1	0.3 (0.1–0.8)	0.016

Finally, we combined the results of the two sets of analyses to predict the probability of being depressed at 6-month follow-up. Those patients depressed at the pre- and postprogram time points and possessing the highest risk profile as defined above had a predicted probability of 85% for being depressed at 6-month follow-up. Those depressed at neither initial time point and possessing the lowest risk profile as defined above had a predicted probability of 7% for being depressed at follow-up. The relatively small increment to predicted risk obtained by adding the risk profiles to the screening results (7 vs. 10% and 84 vs. 73%) demonstrated the predictive power of the two-stage screening results and suggested that there is little to be gained by incorporating the risk profile into the two-stage process.

If it is not possible to implement a two-stage screening process, knowledge of the risk factors for being persistently depressed can significantly improve a single-stage screening process. For example, patients who were depressed at time one and had the highest risk profile (type 2 non-insulin-treated, multiple complications, no high school degree) were at the same (predicted) risk of being depressed at follow-up as those who scored positive at both stages of the two-stage screening process (72 vs. 73%). Those who had one or two factors from the high-risk profile in addition to an initial positive screening score were at intermediate risk of being depressed at follow-up (>50%).

CONCLUSIONS — Although >33% of all patients experienced depression symptoms initially, only 33% of those remained disturbed over the 6-month study period. This study was undertaken to determine whether the predictors of persistent disturbance were different from factors predicting one-time disturbance in the earlier study (2). Several potential predictors produced congruent results for both initial and persistent depression symptoms. Lack of education and the presence of multiple complications were associated with more disturbance at program entry, and with higher rates of persistence. Other factors, such as HbA_{1c} and duration of diabetes, were not associated with initial or persistent disturbance. On the other hand, several factors (race, sex, age, and marital status) were related to initial level of disturbance but not to persistent disturbance. The type of diabetes, which was not associated with initial disturbance, was associated with persistent disturbance. These results suggest that there is a difference between factors that predict high initial symptom levels and those that predict persistent symptoms.

It is known that a depression symptom level at a single time point is not an accurate predictor of psychiatric diagnosis, because symptoms must be persistent for the diagnosis to be made. Therefore, persistent depression symptoms fall in the category of a psychological disturbance that more closely approximates a diagnosable psychiatric disorder. Conversely, transient depression symptoms may reflect a situational response to life circumstances. Several psychosocial factors were associated with transient depression symptoms but not persistent depression symptoms; these factors may be associated with the prevalence of transient stressors or may influence vulnerability/resistance to those stressors. For example, race may be associated with sporadic incidents of discrimination, and being married may allow one to manage episodes of stress more effectively. On the other hand, biological disease-related factors were more strongly associated with being persistently depressed than with being depressed at a single time point. This finding may reflect the existence of a biological component to persistent depression symptoms that makes that constellation of symptoms more similar than transient psychological distress to full-blown depressive psychiatric disorder.

Disease type played a larger role in being persistently depressed than in transient depression symptoms. There was a monotonic decrease in the proportion of patients with persistent depression symptoms when moving from low to high insufficiency of endogenous insulin. This may reflect a common metabolic derangement shared by diabetes and persistent depression symptoms (12–14). However, it is

not clear how this pattern fits with the hypothesized biological mechanisms. Nevertheless, the similarity between type 2 insulin-treated patients and type 1 patients suggests that it is inappropriate simply to compare type 1 and type 2 diabetes. Failure to distinguish subgroups of type 2 diabetes calls into question findings of no difference for depression between types of diabetes (15).

Complications of diabetes, another biological risk factor, also had an association with being persistently depressed that approximated the association with being initially depressed (2). Although the presence of sequelae preceded the measurement of persistent depression symptoms, this did not justify a claim of causal precedence, because we did not know the time of onset for the complications and persistent depression symptoms. Either could precede the other. Although the onset of medical conditions can trigger depression (through either psychological or biological processes), the reverse is also true—depression increases risk for subsequent medical disorders (16,17). Even though the causal dynamics are not clear, the presence of medical complications does help to identify a subgroup at high risk for being persistently depressed.

This study demonstrated that initial levels of depression symptoms predict later levels of depression symptoms. Preprogram and postprogram levels were roughly equal in overall predictive power. Preprogram depression symptoms had greater sensitivity and NPV, in part because more patients were captured (i.e., there was a higher positive rate). Conversely, postprogram depression symptoms had greater specificity and PPV because patients who could not be restored to a nondepressed state by the intervention had a more recalcitrant condition that was likely to persist. Combining the pre- and postprogram scores but retaining only two risk levels did little to improve prognostic accuracy. Increased accuracy required three risk levels, because combining the intermediate risk group with either high- or low-risk groups yielded no increase in prognostic accuracy.

The prognostic value of the initial screening results can be assessed by comparing the results obtained to the more conventional use of the reported statistics. The traditional use of the screening results is to compare the method being evaluated with a "gold standard," such as a clinician's diagnosis. When the CESD has been used in this type of procedure, its sensitivity has fallen into a range of 0.65–0.85, compared with our results of 0.47–0.78, and specificity has been in a range of 0.55–0.90, compared with our results of 0.72–0.93 (18). Thus the ability of the CESD to predict later depression symptoms approached the limit of its ability to predict a concurrent diagnosis of depression.

This study suggests a two-step process for screening depressive symptoms in conjunction with education programs (and perhaps other settings). If patients score negative for being depressed at the initial screening, their risk of becoming depressed over 6 months is low (12% in our study) and postprogram screening will yield relatively little; these patients may not need further follow-up. If patients score positive at initial screening, they should be followed with a second screening at the end of the brief intervention period. Patients who score positive again are at a very high risk for being persistently depressed (73% in our study) and should be offered a referral to a mental health provider for a diagnostic workup and/or intervention. Patients who score negative at the second screening are not feeling depressed at that time but still have an elevated risk for being depressed later (37% in our study); they should be screened again later and offered an intervention if the need manifests itself.

Another application of the two-stage screening methodology can be derived from the results of this study. The two-stage process can be used if a patient is screened at two time points over a relatively long period of time, perhaps between regular appointments 3–6 months apart. The same decision rules outlined for the short-term two-stage process can be applied.

If it is not possible to implement a two-stage screening process, a single-stage process can incorporate knowledge of the risk factors for chronic depressive symptoms to calculate a risk score. The following estimates of risk are based on our study population and may not be generalizable to all diabetic patient populations, but we provide them here for their potential practical value. The baseline risk of being depressed at follow-up was ~10% for those who had no risk factors and did not screen positive for depressive symptoms. Screening positive for depressive symptoms added ~30% to the patient's predicted risk of being depressed at follow-up, and each of the three factors from the risk profile added ~10%. Although this approach does not yield the same clear categories with straightforward practical implications, it can be useful when a second screening result is not available. The risk factors identified here are commonly available from patient charts or can be ascertained quickly and easily during medical interviews.

Although the percentage of diabetic patients with persistent depressive symptoms was low compared with the rate of transient symptoms, these patients represented an important clinical subpopulation. These patients are unlikely to improve without an intervention specifically for their depressed state. Their quality of life suffers even if their immediate physical health does not. Research has shown that health care providers without psychological/psychiatric training often fail to diagnose clinical depression (19,20). This is unfortunate, because effective treatment for depression is available (21,22). The appropriate use of screening instruments in diabetes education and care settings may help providers to identify candidates for treatment and/or referral to health care providers with mental health expertise, thereby controlling or preventing mental and physical health problems.

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Patrick Lustman suggested the focus on persistent depression.

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