Treating Depression to Prevent Diabetes and Its Complications: Understanding Depression as a Medical Risk Factor

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Depression has been associated with diabetes for > 300 years,[1] and the durability of this connection is likely related to a conspicuous presence of depression in diabetes practice settings. Symptoms of depression severe enough to warrant treatment are encountered in one of every four patients with diabetes.[2] The affective illness tends to follow a chronic or highly recurrent course, not unlike hypertension, with the rate of depression recurrence in the 5-year period after successful treatment approximating 90%.

In this article, the authors describe the sweeping adverse effects of depression. An argument is made that depression can be viewed as a modifiable independent risk factor for development of type 2 diabetes and for progression of complications from either type 1 or type 2 diabetes, risks not unlike those imposed by age, obesity, or physical inactivity. Framing depression treatment partly for its potential to preserve physical health, functioning, and independence may enhance acceptance of depression treatment by people with diabetes and their providers, ultimately improving medical outcomes.

GLOBAL IMPACT AND BURDEN OF DEPRESSION

Depression is a devastating disease that adversely affects all aspects of one's existence. It is a pervasive disorder that afflicts individuals of all ages, cultures, and races. Nearly 340 million people worldwide, including 18 million in the United States, suffer from depression.[3] Effective therapies for depression are available, including medication and counseling, but < 25% of depressed people have access to these treatments.[4]

In 1992, the World Health Organization, World Bank, and Harvard University initiated the Global Burden of Disease Study.[5] A primary impetus of the project was to evaluate the burden of > 100 common diseases, utilizing measurements that integrate nonfatal health outcomes. The study clearly demonstrated the global impact of neuropsychiatric illness.

As shown in Figure 1, depression was the fourth leading cause of disability in 1990 and was predicted to become the second leading cause of disability by 2020. In developed nations, major depression already was a primary cause of disease burden, exceeding all diseases except ischemic heart disease. The disability conferred by depression has been compared to functional impairment from blindness or paraplegia.[6]

IN BRIEF

Current diabetes practice guidelines emphasize the need to augment conventional diabetes therapy with other evidence-based treatments that support improved diabetes outcomes. Clinical depression, much like obesity, is a significant independent risk factor for developing type 2 diabetes and for progression and mortality from type 1 or type 2 diabetes. Effective treatments for depression are available, may enhance glycemic control and insulin sensitivity, and thereby may preserve the physical health and independence of people living with diabetes.

Suicide was the 11th leading cause of death in the United States in 2000 and outnumbered homicides by a ratio of five to three.[7] Mortality from suicide can be conceptualized as an end-stage process of depressive disorders. The prevalence of suicide increases with age, and older adults, especially elderly white men, have a higher rate of suicide than any other age group.[8] More than 90% of those who commit suicide have depression, substance abuse, or another mental disorder;[9] 70% visit their primary care physician within 6 weeks of suicide. Some case-control studies suggest a correlation between burden and severity of comorbid medical illness and suicide.[10]

Depression also is associated with increased medical morbidity and mortality. For example, post–myocardial infarction patients with depression have significantly higher risk of future coronary events and cardiovascular mortality compared to nondepressed patients, even after controlling for differences in demographic characteristics and cardiovascular disease severity.[11] A meta-analysis by Cuijpers and Smit[12] examined 25 studies with 108,628 participants, of whom 6,416 were depressed. The study concluded that depression increases all-cause mortality, with the relative risk of dying being 1.8 times higher in depressed compared to nondepressed people. The information presented thus far underscores the extensive adverse effects of untreated depression, including decreased capacity and functioning, increased risk of suicide, and increased medical morbidity and mortality from all causes.

Estimate 1990		Projection 2020	
Rank		*Rank*	
1	Lower respiratory infections	1	Ischemic heart diseases
2	Diarrheal diseases	❷	**Unipolar major depression**
3	Perinatal conditions	3	Road traffic accidents
❹	**Unipolar major depression**	4	Cerebrovascular disease
5	Ischemic heart disease	5	Chronic obstructive pulmonary disease
6	Cerebrovascular disease	6	Lower respiratory infections
7	Tuberculosis	7	Tuberculosis
8	Measles	8	War
9	Road traffic accidents	9	Diarrheal diseases
10	Congenital abnormalities	10	HIV infection

Figure 1. Global burden of depression ranked according to disability-adjusted life years and in relation to two time points (1990 and 2020). Adapted from Ref. 5.

IMPACT OF DEPRESSION ON DIABETES

Depression Doubles the Risk of Developing Type 2 Diabetes

The increased prevalence of depression in diabetes is explained partially by the fact that depression is an independent risk factor for development of type 2 diabetes. In a recent report, Freedland[13] analyzed data from four large prospective population studies from the United States and Japan that determined the risk of diabetes development attributable to depression. The studies included nearly 100,000 participants in all, and each of the studies controlled for traditional diabetes risk factors in determining risk. While acknowledging the possibility of publication bias and other confounding influences, Freedland concluded that the studies provide convergent evidence that depression significantly increases the risk of developing type 2 diabetes. These findings are corroborated by the fact that major depressive disorder (MDD) typically precedes the diagnosis of type 2 diabetes when interview techniques are used to date the onset of each disorder.[14]

Depression Increases the Risk and Accelerates Development of Diabetes Complications, Particularly Macrovascular Disease

The association of depression with micro- and macrovascular complications of diabetes has been examined in numerous studies. de Groot et al.[15] conducted a meta-analysis of 27 studies to determine whether an association existed between depression and diabetes complications. Depression was associated with small to moderate effect sizes on most complications (retinopathy, nephropathy, neuropathy, and macrovascular disease). Most of the studies included in the analysis used cross-sectional correlational designs, and thus the meta-analysis was not able to establish cause-and-effect relationships.

To assess the potential causal contribution of depression to diabetes complications, Clouse et al.[16] conducted a longitudinal study examining the impact of depression on the onset of coronary heart disease (CHD) in women with diabetes.[16] The subject group was followed for up to 10 years, and active major depression at the initial evaluation independently predicted a significantly increased risk of clinically evident CHD (Figure 2). In the women with depression, onset and prevalence of CHD were affected.

Risks imposed by depression in diabetes also include risk of premature death. Zhang et al.[17] used survival methods to analyze data collected over 10 years on subjects in the National Health and Nutrition Examination Study. Diabetic individuals with total scores ≥ 16 on the Center for Epidemiologic Studies Depression (CES-D) Scale had an accelerated rate of death during follow-up when compared with diabetic people with scores < 16 (Figure 3). After controlling for demographic, lifestyle, and health status factors, the depression group had a 54% greater mortality than the nondepressed group.

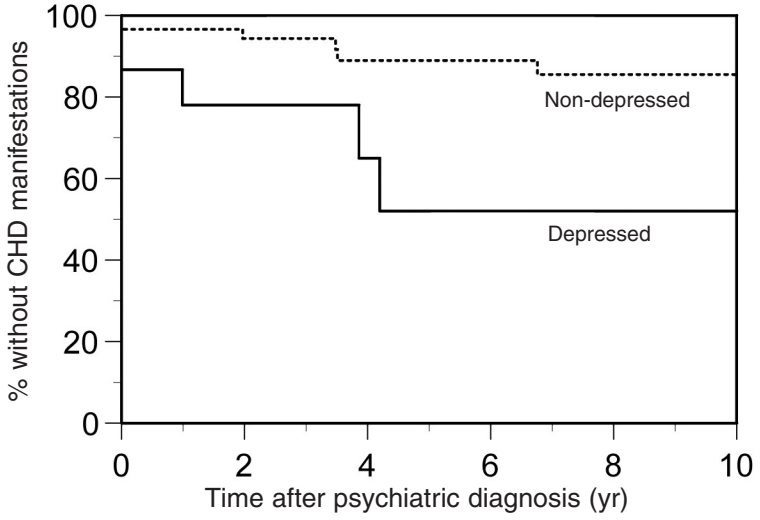

Figure 2. Kaplan-Meier plots showing the development of clinically manifest CHD in relation to depression status. Depressed subjects met criteria for major depression at the time of the index interview. The curves were significantly different across the 10 years (P < 0.01). Risk imposed by depression was independent of usual CHD risk factors at presentation. Adapted from Ref. 16.

The relationship of depression with complications and premature death necessarily translates into high economic burden to individuals and to society. People with diabetes have per capita and out-of-pocket medical expenditures two to five times greater than those without diabetes.[18] However, with exclusion of mental health expenditures, individuals with comorbid depression and diabetes have persistently greater health care utilization and costs (21% greater non–mental health–related payments) than diabetic claimants without depression.[19] Furthermore, hospitalized patients with diabetes and depression also have longer lengths of stay than nondepressed patients with diabetes.[19]

Mediators of Depression Effects on Diabetes Development and Progression

The mediators of depression effects on diabetes development and progression are summarized in Table 1.

Depression is linked with hyperglycemia in most studies of diabetic subjects, a relationship that is corroborated by meta-analyses of the literature in both type 1 and type 2 diabetes.[20] Depression-hyperglycemia associations similar to those reported by Lustman et al.[21] (Figure 4) have been found in other cross-sectional[22–24] and prospective[25] clinical studies and in depression treatment trials.[26–28] Because of the risk imposed by depression on the occurrence and progression of diabetes, it is likely that mediators of this depression-hyperglycemia relationship are largely responsible.

Depression adversely affects a number of behaviors that could be relevant, including dietary behavior, tobacco use, physical activity, cognitive functioning, and adherence to medical treatment.[29] However, behavioral factors alone have been insufficient to explain the importance of depression in influencing outcomes. In a recent study of patients with type 1 diabetes, Lustman et al.[21] again confirmed the significant hyperglycemic effect of depression when controlling for weight and insulin dose. Measures of dia-

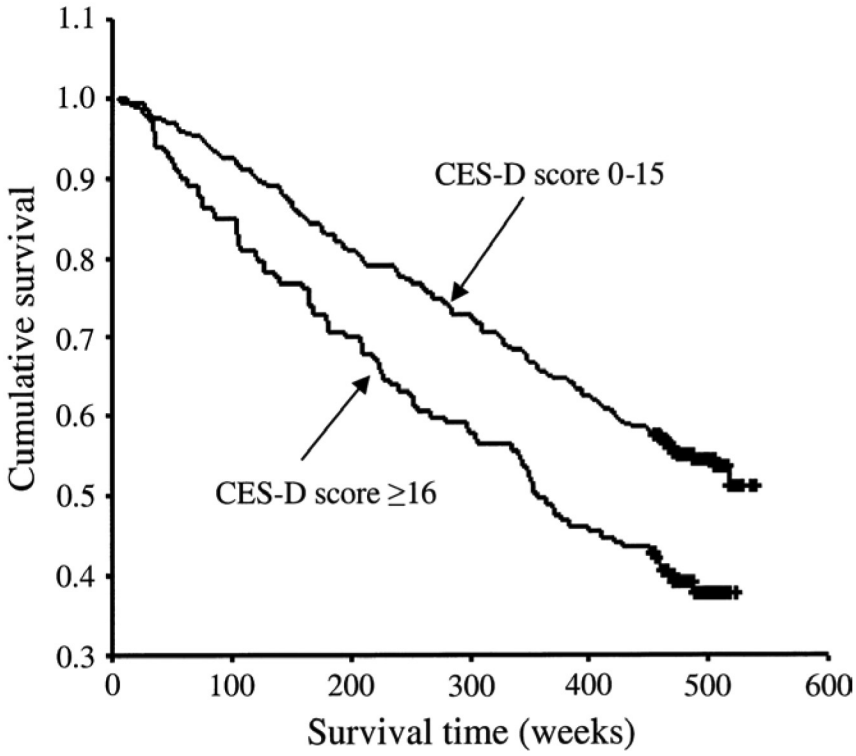

Figure 3. Survival functions in a diabetic population of those with and without severe depression as defined by total scores ≥ 16 and < 16, respectively, on the CES-D. Survival was significantly different between groups. Figure reprinted with permission from Ref. 17.

Table 1. Potential Mediators of Depression Effects on Risk and Progression of Diabetes

Potential Mediator	Depression Effect
Obesity	↑ Weight
Physical inactivity	↑ Fatigue ↓ Social involvement ↓ Physical functioning
Tobacco use	↑ Use
HPA axis hyperactivity	↑ Plasma CRF and cortisol levels
Glucose regulation	Hyperglycemia Increased insulin resistance
Autonomic tone abnormalities (↑ sympathetic, ↓ parasympathetic)	↑ Norepinephrine metabolites ↓ Heart rate variability
Inflammation	↑ IL-6, TNF, and other cytokines
Genetics	Shared genes by depression and insulin resistance

CRF, corticotropin releasing factor; HPA, hypothalamic-pituitary-adrenal; IL-6, interleukin-6; TNF, tumor necrosis factor. Adapted from Ref. 61.

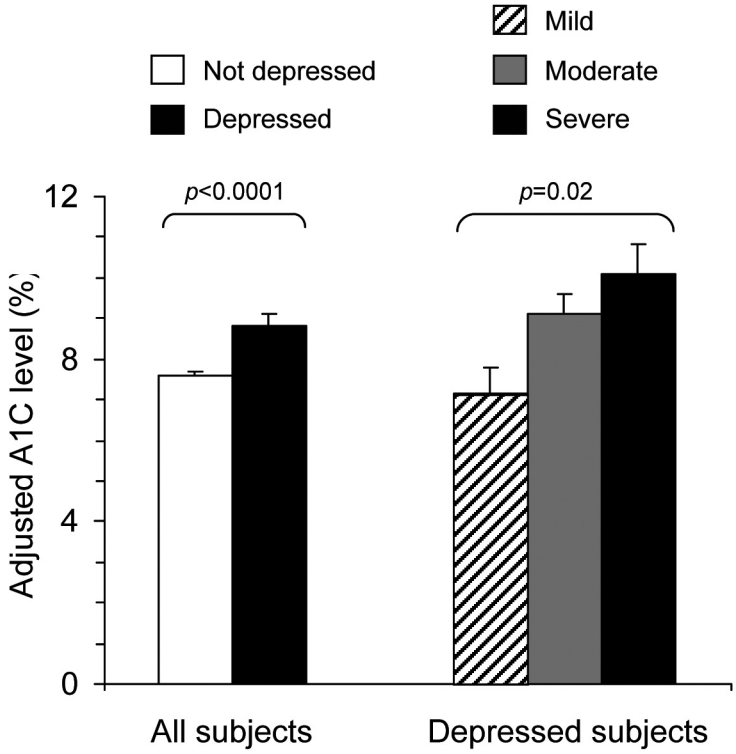

Figure 4. Mean A1C level in relation to depression status after adjusting for weight and total daily insulin dose. A1C results were significantly higher in depressed compared to nondepressed subjects and showed a stepwise increase in relation to depression severity within the depressed subject group. Extensions represent SE. Reprinted with permission from Ref. 21.

betes self-care, when added to the analysis, did not appear to mediate this effect. The authors concluded that although adherence to diabetes self-care may importantly influence metabolic control, other physiological mechanisms must be operational in explaining the hyperglycemia associated with depression.

Physiological features of depression (e.g., glucocorticoid dysregulation, increased sympathetic activity, and alterations in inflammatory processes) may contribute directly to hyperglycemia.[30–33] These factors increase insulin resistance (IR), a potential explanation for a role of depression in the development of type 2 diabetes, the hyperglycemia associated with depression in type 1 diabetes, and the acceleration of diabetes complications.[29] IR has an effect on macrovascular disease that is independent of hyperglycemia, emphasizing the diverse adverse effects that depression could have in diabetic patients. Although information directly tying IR to the risk of diabetes and its complications is lacking, evidence for depression-associated IR is mounting. Elevated blood glucose levels and insulin responses to oral glucose tolerance testing have been demonstrated in depressed subjects with and without diabetes.[34,35] Findings from clinical trials show that relief of depression can be accompanied by parallel improvements in glycemic control[26–28] and IR.[36] Because of its broad association with inflammatory markers including interleukin-6 and tumor necrosis factor-α,[37–39] depression may influence cellular modulation of the stress response, including effects on the transcriptional factor nuclear factor-κβ, which regulates proinflammatory cytokines, adhesion molecules, and chemokines.[40]

Consequently, a direct effect of depression on IR could importantly mediate the depression-hyperglycemia association, but the above studies have not established this causal relationship. Consideration also should be given to the possibility that depression and IR have a common underlying etiology, e.g., genetic. Chiba et al.[41] found that specific tyrosine hydroxylase gene microsatellite polymorphisms were shared between nondepressed subjects with IR and depressed subjects. Further work establishing the correct relationships is essential in positioning depression as the modifiable risk factor. Outcomes from short- and long-term treatment trials already are available, however, to suggest that depression treatment can reduce depression-associated metabolic derangements.

RECOGNITION AND DIAGNOSIS OF DEPRESSION

Most patients with depression seek care from a primary care physician rather than a mental health specialist, and primary care physicians must be able to recognize and treat the disorder, particularly in patients with medical illnesses such as diabetes. Proper depression management is hindered by several barriers, and nearly two-thirds of depressed diabetic patients do not receive antidepressant treatment.[42] Unfortunately, physicians freely attribute depression to the hardships of diabetes and its complications, believe it a justifiable outcome of the medical disorder, and do not offer specific therapy.[42,43] Treatment may be limited to diabetes education and emotional support, suboptimal therapies that are similar to placebo in effectiveness.[27] Another barrier is imposed by poor knowledge of the essential diagnostic elements of psychiatric disorders or concern over the reliability of a diagnosis in the face of diabetes.

Criteria for diagnosis of MDD are provided in the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) and summarized in Table 2.[44] The criteria remain valid in diabetic patients, despite the potential for overlapping symptoms between depression and dia-

betes.[45] At least five of the following key symptoms must be present for ≥ 2 weeks: depressed mood, decreased interest or pleasure in activities (anhedonia), significant change in weight or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, difficulty concentrating, feelings of guilt or worthlessness, or suicidal ideation. One of the symptoms must be depressed mood or anhedonia.

Minor depression involves symptoms below criteria for MDD and impairs function and quality of life. Dysthymia is defined as the presence of less than five symptoms lasting at least 2 years.[46] When discussing depression in diabetes, it is important to consider the concept of "clinically relevant depression."[2] This refers to depression that interferes with functioning and is severe enough to warrant clinical intervention, including MDD, minor depression, and dysthymia, because all forms of depression can impair function and quality of life.

A patient may have multiple symptoms of a depressive disorder, but the symptoms may not be revealed if the clinician fails to ask appropriate or sufficient questions.[47] In the managed care environment, physicians generally do not have the time to perform formal psychodiagnostic interviews. Brief paper-and-pencil screening instruments for detecting depression, such as the 21-item Beck Depression Inventory (BDI)[48] or the 9-item Patient Health Questionnaire (PHQ),[49] can help with this problem (Table 3). Such measures do not require an interview, are self-administered, take < 10 minutes to complete, and are easily scored by summing the ratings of the individual items. We recommend that patients with depressive symptoms lasting at least 2 weeks and total scores of ≥ 16 on the BDI or ≥ 10 on the PHQ undergo formal diagnostic testing to further screen for MDD. Scores ≥ 9 or ≥ 6 on these instruments, respectively, merit further patient questioning as to the clinical relevance of the symptoms.

Table 2. Diagnostic Criteria for MDD*†

1. One of the following:
   - Depressed mood
   - Markedly diminished interest or pleasure in almost all activities
2. Four of the following:
   - Significant weight loss or gain
   - Insomnia or hypersomnia
   - Psychomotor agitation or retardation
   - Fatigue, loss of energy
   - Feelings of worthlessness or guilt
   - Impaired concentration or indecisiveness
   - Recurrent thoughts of death or suicide
3. Symptoms must be present most of the day.
4. Symptoms must be present nearly daily for ≥ 2 weeks.
5. The symptoms must be the source of significant distress or impairment and not be attributable to medications, medical conditions, or bereavement.

*All five criteria are required.
†Adapted from Ref. 44.

MANAGING DEPRESSION TO DELAY DEVELOPMENT OR SLOW PROGRESSION OF DIABETES

Improvement in Glucose Regulation With Successful Depression Treatment

Hyperglycemia, reflected as elevated hemoglobin A_{1c} (A1C) levels, and IR are principal independent determinants of diabetes complications. Accordingly, interventions directed at these end points are the mainstays of diabetes therapy. To prevent complications, the American Diabetes Association (ADA) recommends that A1C results be maintained ≤ 7.0% (~ 1.0% above normal).[50] In practice, however, most diabetic patients do not achieve this degree of control, even with intensive treatment and systematic follow-up.[51] For this reason, the ADA's annually published statement on "Standards of Medical Care in Diabetes"[50] advocates augmenting conventional glucose-lowering therapy with other evidence-based interventions that support improved diabetes outcomes. Treatment of major depression provides an example of such interventions.

To monitor effects of depression treatment on glucose regulation, treatment studies have measured changes in A1C and markers of IR in relation to intervention and to depression response. In an early study, therapeutic doses of nortriptyline were administered to depressed and nondepressed patients in a double-blind placebo-controlled manner.[26] The design allowed for identification of independent contributors to change in A1C levels. Path analysis indicated that the direct effect of nortriptyline was to worsen glycemic control,

Table 3. BDI and PHQ Depression Screening Tools

Information on obtaining and using the PHQ and BDI can be found online at:
PHQ:
http://www.pfizer.com/pfizer/phq-9/index.jsp
BDI:
http://harcourtassessment.com/haiweb/Cultures/en-US/default.htm

whereas the treatment-independent effect of depression remission was a reduction of 0.8–1.2% in A1C. In a subsequent study, fluoxetine-treated diabetic patients showed a trend toward greater reduction in A1C results after 8 weeks of therapy (−0.40 vs. −0.07% for placebo, $P = 0.13$).[26] Although the reduction in A1C level was not linked conspicuously to improved depression symptoms, the study design was less able to distinguish drug and depression-remission effects. In both investigations, effects on A1C were unrelated to changes in weight. In a recently completed study, bupropion improved depression in > 80% of patients with type 2 diabetes enrolled in an open-label trial. Weight loss and depression improvement accompanying treatment independently predicted improvement in A1C results.[52]

A study of cognitive behavior therapy (CBT) removed potential for medication effects and assessed depression and A1C end points after 10 weeks of treatment and again after 6 months.[27] No differences were observed in covariate-adjusted A1C results at the conclusion of treatment between active and control groups, despite important differences in depression response. However, at 6-month follow-up when CBT effects on depression appeared sustained, covariate-adjusted A1C results were lower in the active therapy group (9.5 vs. 10.9%, $P = 0.03$). Okamura et al.[36] compared 20 nondiabetic patients with depression to an age-, sex-, and BMI-matched nondepressed control group using frequently sampled intravenous glucose tolerance testing (FSIGTT) to assess IR. S_i, the index of insulin sensitivity determined from FSIGTT (expressed as $10^{-5} \cdot min^{-1} \cdot pmol^{-1} \cdot l$), was significantly lower in depressed than in nondepressed subjects (6.0 ± 2.5 vs. 13.8 ± 8.6, $P = 0.0005$). This confirmed the association of depression with increased IR in nondiabetic individuals.

Depressed subjects also were compared before and after depression treatment. Each patient was prescribed a tricyclic antidepressant (TCA), allowed a food intake of 1,800–2,200 kcal per day, and underwent no exercise therapy. A significant increase in S_i was observed after treatment (to 10.7 ± 7.5, $P < 0.01$) with no concomitant alteration in BMI, fasting blood glucose, or other indexes of glucose effectiveness.

Overall, the changes observed in these trials suggest that successful depression treatment may have favorable effects on glucose regulation, effects that might improve the course of diabetes and, if generalized to people with prediabetes, delay development of diabetes. The mechanism behind these improvements is not fully elucidated. Remission of depression may have beneficial effects on health-related behaviors, such as physical activity, medication adherence, and dietary habits, or via effects on physiology involved in glucose metabolism.[30]

Short- and Long-term Management of Depression in Diabetes

Acute relief of MDD typically requires specific therapeutic intervention; the rate of improvement in response to nonspecific supportive measures is not different from placebo. As described in the previous section, both pharmacological and psychotherapeutic interventions are effective for depression in diabetic patients.[26–28,53] Antidepressant medication is the treatment of choice in the primary care setting largely because it is less labor intensive than psychotherapy, has lower initial costs, and mimics the form of treatment received in this setting for most other medical problems.

Having a more favorable adverse effect profile and efficacy equal to or better than TCAs, the selective serotonin reuptake inhibitors buproprion, mirtazapine, and venlafaxine are recommended as first-line treatment of depression in diabetes.[26,28,53] Bupropion has relatively little effect on weight or sexual functioning, factors that may enhance acceptance of depression treatment, particularly maintenance regimens.

Pharmacological management of depression in patients with diabetes demands awareness of common comorbid conditions, potential drug-drug interactions, and adverse effects. Because of these concerns, medications such as monoamine oxidase inhibitors and TCAs are not commonly used to treat diabetic patients. TCAs are associated with orthostatic hypotension, urinary retention, and prolongation of cardiac repolarization leading to QT interval prolongation. TCAs should be avoided in patients with cardiac conduction defects and cardiovascular disease. Thus, a significant proportion of diabetic patients are excluded from TCA use because of presumed or diagnosed cardiovascular disease. An integral component of evaluation of depression in patients with diabetes is a review of medications to assess for drugs that can contribute to depression (e.g., some antihypertensive, antineoplastic, and immunosuppressive agents).[54]

Electroconvulsive therapy (ECT) is safe and efficacious in people with and without diabetes. It is most commonly performed on an outpatient basis and frequently provides rapid symptom improvement.[55] Recent research indicates that ECT has no adverse effects on glycemic control in diabetic patients and is safe in this population.[56] ECT is an appropriate treatment modality in diabetic patients with intolerance to medication, medication-refractory depression, or severe and life-threatening depression.[55]

With CBT, patients are taught to recognize and remove patterns of thinking that characterize and perpetuate depression (e.g., "I am terrible, my life is terrible, and I have no future"). The approach is time-limited (usually < 16 weeks); widely used to treat anxiety, depression; and problems with social functioning; and has demonstrated efficacy in treatment of diabetic patients with depression. Eighty-five percent of diabetic patients who received 10 weeks of CBT achieved remission of MDD (a 57% increase compared to control subjects), and 70% remained free of depression at the 6-month follow-up.[27]

The short-term treatment approaches discussed thus far are effective in bring-

ing depression under control. At that point, treatment often is discontinued in practice, possibly because the patient or provider desires to relegate the problem to the past or to simplify what typically is a complicated medical management regimen. Unfortunately, research has shown that as few as 40% of patients remain free of MDD in the year after successful treatment, with recurrence not infrequently accompanied by deterioration in glycemic control.

Maintenance pharmacotherapy refers to the practice of keeping patients on antidepressant medication beyond the point of depression remission to prevent or delay recurrence.[57,58] The efficacy of this approach recently was demonstrated in a double-blind placebo-controlled trial.[28] After recovery from MDD with open-label sertraline, 152 diabetic patients were randomly assigned to continued sertraline (at recovery dose) or to placebo treatment and followed for up to 1 year or until recurrence occurred. The depression-free interval during follow-up was significantly (three to four times) longer in the group maintained on sertraline. Glycemic control improved during open-label treatment and remained so in both treatment groups during the depression-free interval of maintenance.

Other approaches to maintenance currently are being investigated. Without alteration in weight or body composition, physical activity improves insulin sensitivity, glycemic control, and compliance and provides useful adjunctive treatment for depression.[59] Exercise is a useful intervention to prevent progression of pre-diabetes to diabetes, is safe and efficacious in patients with diabetes, and may be of particular value as prophylaxis against recurrent depression in elderly diabetic individuals.[60]

SUMMARY

Our understanding of optimal treatment for depression in diabetic patients is evolving. At present, it is best understood as a process requiring simultaneous comprehensive care of both medical and psychiatric illness aspects. A recent meta-analysis determined that treatment of depression in diabetes could increase the proportion of diabetic patients in good glycemic control from 41 to 58%.[53] The projected improvement in optimal glycemic control would have significant individual and societal benefits in terms of outcomes related to complications, quality of life, and health care expenditures.

We reviewed here evidence in support of a hypothesis that relief of depression may improve the medical prognosis, delaying development or slowing progression of diabetes. We think it important that both patients and providers recognize the implications of the hypothesis for individuals and for society: the genuine possibility that treatment of depression may promote health, even extend life. At the same time we recognize the limited nature of the evidence presented and the somewhat speculative character of our argument. Apart from its effects on specific diabetes end points, depression remains an important focus of clinical care because of its beneficial effects on mood, functioning, and quality of life.

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