Depression and Chronic Medical Illness: Diabetes as a Model

Larry Culpepper, MD, MPH

That severe depression alone can be lethal is well recognized, and is responded to aggressively. That depression can be just as lethal through its effects on chronic disease outcomes has not been understood, nor does depression and comorbid chronic disease elicit the same aggressive response. Such comorbidity is common; the likelihood of depression increases, often two to three fold, among those suffering from many of the common chronic medical conditions such as coronary artery disease, diabetes, cerebrovascular disease, and arthritis (Table). For example, following a myocardial infarction, depression increases the risk of coronary fatalities from 3% to 16.5% at 6 months, and the risk remains increased more than three fold (from 6% to 20%; adjusted RR = 3.10; 95% CI = 1.90 to 4.30) at 18 months after adjusting for other major risks.1,2

Depression also increases the frequency of poor outcomes among those suffering from diabetes. The interactions between depression and chronic medical illness are complex; in this article, the depression-diabetes model is used as a model in describing the effects and treatment implications of depression complicating chronic medical illness.

DISEASE EPIDEMIOLOGY

Lifetime prevalence of major depression in community based surveys range from 4.9 % to 17.1%, with the point prevalence among patients visiting primary care practices ranging from 4.7% to 8.6%.3,4 The World Health Organization found major depression to be the fourth leading cause of worldwide disease in 1990, causing more disability than ischemic heart disease or cerebrovascular disease; by the year 2020, it is projected to be the second leading cause of disability worldwide.5 Its onset is often in early adulthood, resulting in its potent effect on lifestyle behaviors that might contribute to the onset or worsening of chronic medical illness.

In primary care settings that have not adopted practice approaches to screen and manage depressed patients, repeated studies have demonstrated that 30% to 50% of depressed patients are not recognized. Even when recognized, only approximately 20% of patients receive adequate treatment in primary care settings.6 Fifty percent of those committing suicide have seen their primary care physician within the previous 6 months, often for somatic complaints. The economic impact of major depression is considerable: $43 billion in direct health care use and monetary costs, and $17 billion in lost work annually.7,8 Of clinical importance in considering the interactions between depression and other medical illnesses, depression is usual-
Depression and Medical Illness Involve Complex Relationships

<table>
<thead>
<tr>
<th>Medical Illness Prevalence</th>
<th>Prevalence and Impact of Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>3 times morbid risk⁴²</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>40% increased risk of cardiac events⁴³</td>
</tr>
<tr>
<td>Post-myocardial infarction</td>
<td>33% at 3 months;⁴⁴</td>
</tr>
<tr>
<td></td>
<td>Mortality 4 to 6 x¹</td>
</tr>
<tr>
<td>Post-stroke</td>
<td>20% to 25%⁴⁵</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15%;⁴⁶ Poor glycemic control⁴⁷</td>
</tr>
<tr>
<td>Arthritis</td>
<td>40% to 60% increased morbid risk⁴⁸</td>
</tr>
</tbody>
</table>

ly either a chronic episodic illness, or can simply have a chronic long-term course without spontaneous improvement. Although 50% of individuals recovering from their first episode will have a second episode within 5 years, the rate of such recurrence increases to 80% after the second episode, and to 90% after the third.⁹

Likewise, diabetes is a highly prevalent disease that has demonstrated worrisome increases in the United States and other developed countries in recent years. More than 6% of adults in the United States suffer from diabetes, with about half unrecognized. Annually, about 625,000 new cases are diagnosed.¹⁰,¹¹ The rate of diabetes is estimated to be increased two to five fold in certain minority groups. It is the leading cause of blindness, and accounts for 35% of end stage renal disease. As with depression, a large proportion of patients or either not treated, or do not achieve the tight control of their glucose levels required to delay the onset or progression of end organ diseases including blindness, coronary artery disease, cerebrovascular disease, and renal disease. Total expenditures (1995) attributed to diabetes are $47.9 billion, including $18.8 billion for diabetes, $18.7 billion for chronic complications, $8.5 billion for unrelated conditions, and $1.9 billion for comorbidities.¹²

CAUSAL RELATIONSHIPS BETWEEN DEPRESSION AND DIABETES

The presence of depression appears to substantially increase the risk of diabetes. In the 13-year prospective follow-up reports from a community-based study, major depression was associated with a 2.2 fold increase in the development of diabetes, after adjustment for other risk factors. No similar increase was found associated with milder forms of depressive symptomatology.¹³ An 8-year prospective workplace study of Japanese men found a remarkably similar 2.3 fold increase, also adjusted for other risks.¹⁴ The reverse association, the onset of diabetes leading to the emergence of major depression is not thought to occur.¹⁵ However, in both community and primary care samples, major depression is much more frequent among patients with diabetes. In one recent meta-analysis using 42 studies, the prevalence of comorbid depression was significantly higher in diabetic women (28%) than in diabetic men (18%) and in clinical (32%) compared to community (20%) samples. In controlled studies, the odds of depression in the diabetic group are twice that of the nondiabetic comparison group (OR = 2.0; 95% CI = 1.8 to 2.2) and did not differ by sex, type of diabetes, subject source, or assessment method.¹⁶

The course of depression in patients with diabetes has not received sufficient study. One relevant investigation is a 5-year follow-up study of 25 diabetic patients previously enrolled in a depression treatment trial; patients were referred to primary care physicians for usual follow-up care following the end of the 8-week trial. By the 5-year follow-up, 92% had had at least one recurrence, and on average the group had each suffered 4.8 recurrences of major depression. No patient received long-term relapse prevention therapy for depression. The severity of the initial episode of major depression, and incomplete remission of this episode was linked to recurrence and to the development of diabetic neuropathy.¹⁷

EFFECTS OF DEPRESSION ON DIABETES

The presence of comorbid depression results in increased diabetic symptoms, decreased adherence to the treatment plan prescribed for diabetes, worsened glucose control, increased likelihood of the emergence of diabetic complications, and decreased overall function and well-being. Each of these associations will be considered next.
**Increased Symptoms**

In one study of 188 patients with diabetes, aged 40 to 75 years, the Beck Depression Inventory (BDI) was used to assess depression symptomatology. The BDI score was correlated with the presence of various diabetic symptoms, including dizziness ($r = 0.25$), hunger (0.31), sweating (0.37), frequent urination (0.41), trembling (0.47), hyperglycemic symptoms of thirst (0.47), nonspecific feelings of being ill (0.48), and hypoglycemic confused thoughts (0.48).\(^8\)

Although this study did not specifically sample patients with comorbid major depression, it does illustrate the potential interactions between depression and diabetes at a symptom level. Of note, high BDI scores are associated with both symptoms of hyperglycemia and hypoglycemia, indicating poor control, with both too tight or inadequate glucose control.

In a separate study of 114 patients with diabetes, HgA1c levels were poorly correlated ($r < 0.2$) with 9 of 11 diabetic symptoms, and significantly correlated ($p = 0.04$) only with polyuria. However, depression was moderately correlated with nine diabetic symptoms and had a significant ($p < 0.05$) effect on 2 of 3 hyperglycemic symptoms, 5 of 6 hypoglycemic symptoms, and 2 nonspecific symptoms of poor control. The authors concluded that symptoms often attributed to diabetes are more related to depressive mood than to blood glucose control. Thus, depression may cause worsening of glucose control (see below), but it also results in diabetic symptoms being unreliable indicators of poor metabolic control in depressed diabetics.\(^9\)

**Worsened Glucose Control**

One recent meta-analysis of 24 studies found a significant relationship ($z = 5.4, p = 0.0001$) with a small to moderate effect size (ES = 0.17; 95% CI = 0.13 to 0.21) between depression and worse glucose control in diabetics. A second literature review identified 5 studies that assessed the relationship of comorbid depression with glucose control among diabetic patients. In these, depression was associated with a 1.8% to 3.3% increase in HgA1c.\(^17\)

The potentially complex relationship among glucose control, depression, and diabetic care in primary care settings was illustrated by a recent Dutch study.\(^18\) In this study, those scoring low on a neuroticism scale were more likely to be depressed if they had high HgA1c levels, in contrast to those scoring high on a neuroticism scale (who, even with elevated HgA1c levels, were not more likely to be depressed). In those with low neuroticism, the likelihood of depression increased 36% (RR = 1.36) with each 1% increase in HgA1c. The importance of this is reflected in the relationship between HgA1c and outcome; a 1% increase in HgA1c is associated with a 30 mg average increase in blood glucose, and a 35% increase in subsequent retinopathy and other complications.

**Diabetic Complications**

Neuropathy, retinopathy, and nephropathy have all been associated with increased rates of depression.\(^20\) In one study, 74% of patients with complications scored within the range of clinical depression on the BDI.\(^21\) In this study, the severity of depression also was significantly associated with diabetic complications; 35% of patients with complications scored within the range of severe depression. Increased suicidal ideation is also concentrated among those with complications. These findings were confirmed by a recent meta-analysis of 27 studies. In it, depression was significantly associated with diabetes complications (diabetic retinopathy, nephropathy, neuropathy, macrovascular complications, and sexual dysfunction) with effect sizes in the small to moderate range ($r = 0.17$ to 0.32).\(^22\) Because many of the studies involved in exploring these relationships are cross-sectional, the cause effect relationships are uncertain, but likely to be bidirectional.

**Well-being**

The overall well-being of diabetic patients in relationship to their depression status has received little attention from investigators. However, in the Medical Outcomes Study, the impact of both depression and diabetes were assessed. In contrast to a well-being (general health) score of 75 for those with no chronic condition, those with diabetes scored 64 and those with depression scored 59. Although these investigators did not give a score for those affected by both conditions, they did report that the relation-
ship was additive.23 These findings have been substantiated by recent studies of the quality of life of diabetics, in which depression was found to be a powerful predictor.24-26

**CARE OF COMORBID DIABETES AND DEPRESSION**

**Recognition**

The primary care physician has the challenge of recognizing two chronic and potentially devastating conditions, both often missed early in their course. As noted above, in typical primary care practice, 50% of patients with each condition go unrecognized. Although the recognition of diabetes can be facilitated by attention to somatic symptoms and recommended periodic glucose screening,10 there is no laboratory test for depression. Given that more than 80% of depressed patients present with somatic symptoms, clinical screening of adults is indicated, as recently recommended by the US Preventive Services Task Force. They suggest asking two simple questions about mood and anhedonia (“Over the past 2 weeks, have you felt down, depressed, or hopeless?” and “Over the past 2 weeks, have you felt little interest or pleasure in doing things?”), and note that these may be as effective as using longer instruments.27 The PHQ-9 is a useful instrument for confirming the diagnosis of depression and assessing severity in those responding positively to the two initial questions.28

**Treatment**

Given the interaction between depression and diabetes and the expression of symptoms by patients, a reasonable management approach to determining treatment priorities integrates the information conveyed by glucose and HbA1c levels with depressive symptom assessment. For those with significantly elevated diabetic measures and depressive symptoms that are mainly somatic (eg, fatigue, sleep disturbance, altered weight), initial treatment might best target improved diabetic control with subsequent reassessment and treatment of depression. For those with primary anhedonia and depressive mood, especially those with only moderately elevated glucose levels, treatment of depression with continued monitoring, but not tightening, of glucose control might be the best initial strategy.

For all patients, initial counseling should emphasize regular exercise, reported to improve both depression and diabetic control, as well as other routine diabetic and healthy lifestyle modifications.29 In determining specific treatment for depression, the physician should be guided both by available evidence and by the effectiveness of any prior treatment for depression. For those that desire it, cognitive behavioral therapy has been demonstrated to be efficacious for depressed diabetics. In a 6-month follow-up trial of cognitive behavioral therapy, the follow-up HbA1c averaged 12.1 among those depressed and 9.2 among those not depressed.30 In comparison to 27% of controls, 85% of those receiving cognitive behavioral therapy (1 hour per week) were in remission at 10 weeks follow-up; at 6 months the rates were 70% compared to 33%. Of note, HbA1c levels in those treated with cognitive behavioral therapy averaged 9.5% compared to 10.9% for controls (all patients received diabetes education from a certified diabetic educator and were provided with glucometers).31 Cognitive behavioral therapy approaches included behavioral strategies to reinvolve patients with pleasurable social and physical activities, problem-solving strategies to resolve stressful concerns, and cognitive techniques to identify and correct distorted or maladaptive thought patterns.

For those patients not desiring or responding to cognitive behavioral therapy, pharmacotherapy for depression is indicated. In choosing the best antidepressant, the physician should consider the potential adverse effects and drug-drug interactions of available agents as well as the potential effects of the agent in treating or worsening other comorbid conditions (eg, diabetic neuropathy, cardiac conditions).32 The tricyclic antidepressants should not be used routinely in diabetics, given their adverse profile and potentially serious side effects. They have been found to produce an initial phase of hypoglycemia in up to 30% of diabetics, followed by hyperglycemia after 6 to 8 weeks and increased appetite and resultant weight gain.20,33,34 They can worsen problems related to diabetes, including orthostatic hypotension, constipation, urinary retention, and delayed gastric emptying in those with autonomic neuropathy. Given the increase in cardiac
conditions among diabetics, the potential for tri-cyclics to induce arrhythmias is also of concern. Among the selective serotonin reuptake inhibitors, sertraline and citalopram have the best characteristics relevant to treatment of diabetics. These agents both have low potential for drug-drug interactions, with minimal clinically significant effects on most CYP450 isoenzymes. Both fluoxetine and paroxetine strongly inhibit the 2D6 isoenzyme, which will lead to increased levels of a number of cardiovascular agents. Given the long half-life of fluoxetine, this can be problematic in treating a diabetic who develops a new cardiac condition. The tendency of paroxetine to cause significant weight gain is a further worry for diabetics; it has been reported to cause a gain of greater than 7% of body weight in up to 25% of patients (not specifically diabetics) receiving it.35

Sexual dysfunction is of particular concern in the depressed diabetic.36 Before starting pharmacologic treatment for depression, the physician should assess sexual functioning (arousal, erection/lubrication, orgasm), determine whether dysfunction exists, and based on the time course and nature of symptoms, whether it is a complication of diabetes, a symptom of depression, or because of another organic or relationship cause. Based on this initial assessment, the importance of the potential for an selective serotonin reuptake inhibitors to affect sexual functioning can be assessed, and plans for follow-up monitoring if needed agreed on.

Impact of Pharmacologic Treatment of Depression on Diabetic Control

The impact of the treatment of depression on glucose control has been reported in several trials. In a 5-year follow-up study using nortriptyline to treat depressed diabetics, the hemoglobin A1c level among those still clinically depressed was 13.3 compared to 11.1 among those not depressed.17

A randomized, double-blind 8-week trial of fluoxetine compared to placebo in depressed diabetics demonstrated a reduction in the BDI of -14.0 versus -8.8 (p = 0.03) and a reduction in the Hamilton Depression Rating Scale (HAM-D) of -10.7 versus -5.2 (p = 0.01). Forty-eight percent of fluoxetine recipients achieved remission compared to 26% of controls. Given the short duration of the trial, full effect of treatment on HbA1c levels would not emerge, however there was a modest improvement (-0.4 versus -0.13, p = 0.13) among those receiving fluoxetine.37

In a trial of sertraline, 28 diabetics with major depression and a HAM-D baseline score of at least 18 (mean of 22.6) received the modest dose of 50 mg per day for 10 weeks. At outcome the mean HAM-D was 4.9, demonstrating effectiveness. Of note, dietary compliance was improved in those originally not compliant, and HbA1c levels improved for 13 of 17 patients with baseline values greater than 8.0 (p = 0.018).38

INTERACTIONS IN THE TREATMENT OF DEPRESSION AND DIABETES

The primary care physician must integrate several interactions between the effects of the treatment of depression and diabetes. These involve patient education, compliance issues, physical activation, and need for long term treatment.

Education

Common goals of education for both depression and diabetes are to promote patients’ ability to manage their diseases, understanding the potential for complications or in case of depression, relapse or recurrence, recognize side effects, and possibly manage use of adjunctive therapies. The physician might need to stage education, attending to the priorities most relevant to the individual patient. For those severely depressed, the physician might need to repeat and expand education as the patient’s depression improves. Even for patients not referred for psychotherapies, the physician might find the cognitive behavioral therapy strategies listed above of use in managing both diabetes and depression.

Compliance

Adherence with antidepressant therapy is a major concern. In one primary care study, 25% to 33% of patients stopped therapy within 1 month, more than 40% stopped within 3 months, and 62% failed to tell their physician. In one meta-analysis, depression increased noncompliance three fold.39 Patients who are depressed, particularly those severely depressed, do not adhere well
to complex diabetic treatment schedules aimed to achieve tight compliance. This can result in increased primary care, emergency services, and hospital care. This might lead physicians to increase the dose of diabetic medications with hypoglycemic consequences, particularly if patient adherence improves as the depression improves. As patients' moods improve, they also might consider their antidepressant medication unnecessary. Patient education and active patient monitoring can be helpful. Depression improvement may lead to improved self-esteem, self-efficacy and diabetic compliance.

**Physical Activation**

Attaining diabetic control may improve vegetative symptoms of depression, and depression treatment may lead to the patient becoming more physically active. Increased physical activity has been demonstrated to improve both depression and diabetes. As these changes unfold, diabetic medication requirements will alter, and the need for the patient to adjust medications and diet, for instance in response to planned exercise, will increase.

**Need for Long-Term Treatment**

Although most patients understand and accept the need for long-term treatment of diabetes, the same might not be true for depression, especially given its episodic recurrent course. Current recommendations are that treatment be continued for 4 to 6 months after the initial lifetime episode of depression, and indefinitely for those having experienced 3 or more episodes. Although long-term treatment of the patient achieving remission to an episode does not guarantee avoidance of recurrence, it does provide major benefit. In one study, only about 20% to 30% (depending on the treatment) experienced recurrence during 3 years, if maintained at full-dose treatment, whereas 70% had recurrences if maintained at half the initial treatment dose, as did 78% of those receiving placebo.

For individuals with comorbid chronic medical illness, including diabetes, the physician should carefully monitor both conditions when a patient's antidepressant is tapered and discontinued. Changes in diabetic control might be an indication of the reemergence of depressive symptoms.

**CONCLUSION**

When occurring in the same patient, depression and diabetes can result in increased symptoms, poor compliance with treatment recommendations, and increased likelihood of lethal complications. Because of the interaction of the effects of the treatment of depression on a patient's diabetic state and treatment, and the inverse, treatment of the two conditions must be integrated to avoid potentially dangerous adverse effects. Many of the principles and tactics described above can be applied to the integration of the treatment of depression and other medical conditions as well as diabetes. Although the primary care physician is in an excellent position to manage both conditions, if consultants are involved or care is managed by two specialists, communication before treatment changes is essential, as is development of a shared treatment plan. Successful treatment can lead to improved outcomes of both conditions.

**REFERENCES**


