Depression is common in medically ill patients, and it presents a particular challenge to the primary care physician. Depression may exacerbate cardiovascular disease, diabetes, and irritable bowel syndrome. Also, it may cause a poorer prognosis of each of these disorders. It is therefore recommended that depression screening be incorporated into a treatment plan for all these conditions, because treatment of depressive symptoms will improve patient quality of life and the outcome of other comorbid illness.

Depression is extremely prevalent in medically ill patients, increasing linearly as one moves from the general population to ambulatory primary care patients to medical inpatients. As shown in Figure 1, comorbidity between depression and various medical illnesses is almost the rule rather than the exception.

The presence of comorbid depression presents a definite challenge to the treatment of patients who come to a primary care practice with cardiovascular disease, diabetes, or gastrointestinal complaints. Depression may compromise the patient’s ability to comply with the medication regimens, dietary restrictions, or lifestyle modifications that are an integral component of the successful management of so many chronic diseases. In addition, depression often heightens somatization of the chronic medical illness. The physician may then order unnecessary tests or additional medication in an understandable but erroneous belief that increased symptoms represent increasing severity of the primary disease.

This review examines the challenges and consequences of depression with concomitant illness. It also examines the increasing body of evidence that suggests depression may actually worsen the physiology of certain comorbid medical conditions. Conditions to be examined include cardiovascular disease, diabetes, and irritable bowel syndrome.

Depression and Cardiovascular Disorders

Poorer Prognosis

Depression is extremely prevalent in patients with cardiovascular disease, and it may have an impact on clinical outcomes. Indeed, depression occurs in 16% to 23% of patients with cardiovascular disease and in almost 1 in 5 patients recovering from acute myocardial infarction (MI). Furthermore, in more than 75% of patients found to have major depression 8 to 10 days after an MI, the affective disorder persisted for at least 3 months after the MI.

The combination of depression and cardiovascular disease can have serious consequences (Figure 2): patients with depression have both increased cardiovascular morbidity and mortality. For example, patients with major depression are four times as likely to die in the first 6 months after an acute MI than are those without depression—a mortality risk factor that approximates other serious risk factors, such as left ventricular (LV) dysfunction and prior MI. These negative effects are independent of severity of coronary artery disease (CAD), MI, LV dysfunction, and other indices of cardiac diseases.

Depression also increases disability in patients with coronary disease and their utilization of medical care. Clearly, the comitant existence of depression in patients with cardiovascular disease confers significant burden, both medical and financial.

An Independent Risk Factor

In addition to studies indicating that depression may exacerbate existing cardiovascular disease, several large, longitudinal studies in disease-free patients have further confirmed that depression is a significant—and independent—risk factor for the subsequent development of CAD. Analysis of the National Health and Nutrition Examination Survey (NHANES) data adjusted for confounding variables demonstrated that for men, depression significantly increased the risk of both cardiovascular morbidity and mortality; women had an increased risk of nonfatal cardiac events.

In another prospective, longitudinal study of more than 1550 subjects without heart trouble, patients with a history of major depression at baseline had a fourfold increase in self-reported MIs 13 years later. Again, this increased risk was independent of other coronary risk factors.

Physiologic and Behavioral Mechanisms

Understanding the potential mechanisms through which depression increases the risk for the development of cardiovascular diseases may help the primary care physician to appreciate the need to identify and address comorbid depression in patients with such diseases. Indeed,
clinical evidence suggests that specific physiologic changes may be involved. For example, depressed patients who are otherwise healthy have increased platelet aggregation, which is a pivotal etiologic factor in atherogenesis, unstable angina, and MI.\textsuperscript{10} Interestingly, evidence of exaggerated baseline platelet activation has also been found in depressed, otherwise healthy patients\textsuperscript{11} and in depressed patients with ischemic heart disease\textsuperscript{12} compared with nondepressed, healthy individuals. Administration of a selective serotonin reuptake inhibitor has been shown to normalize platelet activity in depressed patients.\textsuperscript{12,13}

Neurohormonal dysregulation of cortisol and catecholamine release associated with depression may also facilitate recurrent endothelial dysfunction and subsequent chronic inflammation, which is now recognized to be a critical factor in the development of CAD.\textsuperscript{10,14} Another possible mechanism is the as yet-undefined relationship between depression and a heightened inflammatory response, particularly in patients with cardiac disease.\textsuperscript{10} These studies are interesting because they suggest that treating depression may have more far-reaching effects on a patient’s physiology than simply correcting mood. Positive benefits may potentially be conferred both in terms of improved immune response, reduced pathologic inflammatory responses, and improved circulatory function.

Although depression is also associated with several major cardiac risk factors caused by lifestyle and behavior (including hypertension, smoking, diabetes, and reduced exercise capacity),\textsuperscript{10} the effect of depression on cardiac prognosis is independent of these risks. Depression may actually potentiate certain risk factors. For example, depression increases the negative effects of smoking, elevated low-density lipoprotein cholesterol (LDL-C), and increased fibrinogen levels.\textsuperscript{10} Diabetic patients with depression are more than three times as likely to have coronary heart disease develop over 10 years than are diabetic patients without depression.\textsuperscript{10,15}

In addition, depression also appears to jeopardize successful self-management of chronic medical disease. Depressed patients are less likely to comply with prophylactic aspirin and other medication regimens, adhere to lifestyle interventions, and participate in cardiac rehabilitation programs than are non-depressed persons recovering from an MI.\textsuperscript{16-18}

Taken together, these studies demonstrate that the negative effects of depression on cardiovascular disease are multifactorial, underscoring the need for increased diagnosis and management of depression in the medically ill by the primary care physician. Such identification and treatment of the exacerbating mental illness may improve outcomes in patients with cardiovascular disease and should be incorporated into an algorithm for care (Figure 3).

**Depression and Diabetes**

*Higher Prevalence of Depression*

The incidence of depression in patients with diabetes is particularly high. Although epidemiologic studies vary widely in their diagnostic criteria and their ability to control for other variables, individuals with diabetes appear to be at least three times more likely to have depression than the general adult population.\textsuperscript{19}

According to a critical review of eight controlled studies, 14% (range, 8.5% to 27%) of adults with either type 1 or type 2 diabetes mellitus have a major depressive disorder.\textsuperscript{19} Approximately 32% of subjects with diabetes in these controlled studies had clinically significant symptoms of depression (range, 21.8% to 60.0%).\textsuperscript{19} In another controlled study, 35% of patients with complications of type 2 diabetes mellitus had...
severe depression as measured by elevated Beck Depression Inventory scores. These elevations were not caused by somatic symptoms of neuropathy, retinopathy, or nephropathy but reflect increases in cognitive rather than somatic portions of the assessment.

**Accelerated Rate of Complications**

Depression may directly worsen glycemic control and accelerate the development of diabetic complications that are at the root of the morbidity and mortality associated with diabetes. In addition, depression significantly decreases adherence to medication and dietary regimens prescribed for glycemic control. Depression has been shown to predict the development of coronary heart disease independently of other risk factors in patients with type 1 diabetes mellitus. A prospective, longitudinal study of children with type 1 diabetes also found that depression increased the risk of retinopathy over 10 years, with the risk increasing the longer depression was present.

In addition to the exacerbation of physical symptoms, the depressed patients in this study were also more likely to incur greater medical costs in primary care and specialty offices, emergency departments, hospitals, and mental health facilities. Total health care costs were 86% higher in diabetic patients who were depressed than in nondepressed diabetic patients. The impact of depression comorbid with diabetes therefore devastates patients both on a physical as well as a financial level.

**A Diabetes Risk Factor?**

Several population-based studies have examined the relationship between depression and diabetes. Eaton et al followed up more than 1800 adults without diabetes at baseline for 13 years; they found that the presence of major depression increased the risk of the development of type 2 diabetes by more than twofold, even when controlling for other potentially confounding factors.

A longitudinal analysis of prospective data from Japanese men found a comparable relationship: men with moderate to severe depression had more than twice the risk of type 2 diabetes developing by 8 years than nondepressed subjects. The increased risk occurred independently of other known diabetes risk factors, including obesity, smoking, drinking, family history of diabetes, and physical inactivity.

These studies suggest depression may at least, in part, contribute to the development of diabetes. Such data suggest that early diagnosis and treatment of depression in patients at risk for the development of diabetes should be incorporated into an overall interventional health care strategy. Primary care physicians may therefore consider depression screening in patients with a family history of diabetes or other predisposing characteristics.

As with cardiovascular disease, several hypotheses about the biologic relationship between depression and diabetes have been suggested, based to a great extent on the relationship between cardiovascular disorders and diabetes mellitus.
Patient has comorbid disorder

- Is patient or a family member reporting basic neurovegetative symptoms of depression?
  - Sad, blue, down, or some other descriptive term
  - Change in sleep habits
  - Food is tasteless, loss of appetite
  - Decrease in motivation
  - Poor concentration
  - Agitation, irritability, worry (inappropriate)
  - Expressing any suicidal ideas or behaviors

  YES

  Indication of possible depression

  Indicator of possible depression

  YES plus “soft signs” in elderly

  Good indication that depression is present

  Subtle cognitive deficits may be missed in casual interview

  Have trained staff administer Mini-Mental Status Examination

- Does patient appear to have multiple somatic complaints for which there appear to be no cause?

- Has patient had difficulties following his or her post-myocardial infarction treatment plan?
  - Is patient cognitively intact?
  - Does patient have a clear understanding of his or her illness? If not, is there a family member who does?

- Are there environmental stressors that could be producing a reaction?

- Are there any known reactions to the patient’s current medications that could account for the changes in behavior?

- Does patient have a risk factor for depression?
  - Prior history
  - Family history
  - History of substance abuse

  YES

  Intercede soon

  Provide referral list

Examples:
- β-Blockers
- Corticosteroids, NSAIDs
- Methyldopa
- Baclofen
- Estrogens
- Benzodiazepines
- Metoclopramide
- Some antibiotics
depression and insulin resistance. Depression is associated with parallel activation of both the sympathetic nervous system and the hypothalamic-pituitary axis, two pathways known to result in increased blood glucose levels and decreased insulin sensitivity.

An evolving line of investigation suggests that depression may actually originate from the same pathogenetic pathway as glucose intolerance. According to this model, abdominal fat accumulation, metabolic abnormalities such as insulin resistance, and hypertension are all linked to a common polymorphism of a glucocorticoid receptor gene. This genetic aberration triggers neuroendocrine and sympathetic nervous system stress reactions, leading to somatic conditions caused by long-term activation of these pathways. Because depression develops along the same pathways, it may very well represent this heightened genetic susceptibility to stress. As such genetic predispositions are further understood, appropriate interventive care may become standard, and may further reduce the development of chronic diseases.

**Antidepressant Therapy in Diabetes**

There exist many published studies of the use of antidepressants in patients with diabetes, both to treat depression as well as to alleviate diabetic neuropathy; these trials are discussed in detail in several comprehensive reviews. Because serotonin reuptake inhibitors or serotonin precursors may decrease blood glucose levels and thus help achieve dual therapeutic goals, these agents are under active clinical investigation in patients with comorbid diabetes and depression.

In addition to addressing a biologic substrate, the benefits of treating patients in this population for depression include an increased capacity for successful self-management and the potential for fewer diabetic complications associated with glycemic control. Those potential benefits include:

- restored sleeping and eating habits;
- improved social, occupational, physical, and other behavioral activity;
- improved pain;
- improved tolerance for pain;
- improved ability to cope with illness;
- improved general functioning;
- decreased preoccupation with somatic complaints;
- enhanced sexual functioning;
- improved adherence to treatment regimen; and
- improved glycemic control.

Again, the benefits of treating major depression can be seen as having medical benefits that extend beyond solely correcting a disturbance in mood.

**Depression and Irritable Bowel Syndrome**

Multiple studies across three decades have documented the pervasive comorbidity between irritable bowel syndrome (IBS) and affective disorders such as depression. According to a review of this body of literature, at least 90% of patients with IBS also have at least one psychiatric disorder, the most common of which is major depression. Depression is more common in patients with chronic or refractory IBS, whereas patients with newly diagnosed disease tend to have anxiety disorders.

An explanation for the comorbidity between IBS and affective disorders is still evolving. Some experts believe it reflects the intensive interaction between the brain and the gut, while others think it calls into question the legitimacy of IBS as a distinct diagnostic entity. It has been hypothesized that future studies may delineate two categories of IBS: one in which the etiology is primarily psychologically versus one in which etiology is primarily biological. Although clinical studies are limited, the brain-gut interaction does provide a clear physiologic rationale for the use of psychotropic medications in the treatment of patients with IBS.

**Comments**

Comorbid depression and medical disorders may pose a significant clinical challenge for the primary care physician, for whom patients with cardiovascular disease, diabetes, and other chronic medical illnesses account for a meaningful component of clinical practice. Given the significant rate of depression associated with chronic medical illnesses and its impact on the outcome and compliance with treatment regimens, screening for depression should be as routine as taking blood pressure and measuring height and weight at an office visit. The challenge, described in detail elsewhere in this supplement, is in being efficient at collecting the information and effective at making the diagnosis and recommendations for treatment.

Knowing the treatment options for depression is no different than knowing the options for any other chronic illness. The more flexibility physicians have to offer patients for managing their depression, the better chance physicians have for improving the outcome of depression and any coexistent illness.

**References**


