Clinical and Health Services Relationships between Major Depression, Depressive Symptoms, and General Medical Illness

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Patients with chronic medical illness have a high prevalence of major depressive illness. Major depression may decrease the ability to habituate to the aversive symptoms of chronic medical illness, such as pain. The progressive decrements in function associated with many chronic medical illnesses may cause depression, and depression is associated with additive functional impairment. Depression is also associated with an approximately 50% increase in medical costs of chronic medical illness, even after controlling for severity of physical illness. Increasing evidence suggests that both depressive symptoms and major depression may be associated with increased morbidity and mortality from such illnesses as diabetes and heart disease. The adverse effect of major depression on health habits, such as smoking, diet, over-eating, and sedentary lifestyle, its maladaptive effect on adherence to medical regimens, as well as direct adverse physiologic effects (i.e., decreased heart rate variability, increased adhesiveness of platelets) may explain this association with increased morbidity and mortality. Biol Psychiatry 2003;54:216–226 © *2003 Society of Biological Psychiatry*

Key Words: Depression, medical comorbidity, function, costs, mortality

Introduction

The United States population is aging substantially. It is estimated that today, 12.5% of the U.S. population is 65 years and older, but by 2050, 20%–25% will be older than 65 years (Olshansky et al 1993). The decline in mortality rate is, in part, a tribute to the improved medical treatment of chronic medical illness, substantially lengthening the lives of patients who suffer from these medical illnesses. One end result of this, however, is that with the aging of our population, physicians will be called upon to treat a higher percentage of patients with chronic medical illness. Eighty-eight percent of people aged 65 and older have one or more chronic medical illness, and one quarter of them will have four or more conditions (Hoffman et al 1996).

This article will review the incidence and prevalence of major depression in patients with chronic medical illness and the association of this affective disorder with symptom burden, functional impairment, adverse health behaviors and adherence to self-care regimens (diet, exercise), satisfaction with care, medical utilization and costs, morbidity and mortality, and possible pathophysiologic mechanisms that may worsen the course of medical illness. This review of the adverse impact of depression will focus on diabetes and heart disease because of their high prevalence and the depth of research describing the impact of depression comorbidity in patients with these illnesses. The literature review for this manuscript included screening English-language articles identified through MEDLINE (1992 to the present) by pairing the word "depression" with the following key words: medical illness, heart disease, myocardial infarction, diabetes, HIV, cancer, stroke, Parkinson's disease, multiple sclerosis, somatization, function, pain, health risk behaviors, smoking, obesity, adherence, costs, and mortality.

Epidemiology of Depression and Chronic Medical Illness

As one moves from community settings to primary-care settings to inpatient medical settings, the prevalence of major depression increases from 3%–5% to 5%–10% to 10%–14% (Feldman et al 1987; Katon and Schulberg 1992; Kessler et al 1994; Myers et al 1984; Rapp et al 1988). Patten (2001) recently described in a longitudinal community-based study in Canada the incidence of new-onset episodes of major depression in subjects with and without long-term medical conditions. Patten (2001) found that there was an increased risk of developing major depression with virtually any long-term medical condition in 4% of those with one or more medical conditions,

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compared with 2.8% of those without medical conditions. Wells et al (1988) in the Epidemiologic Catchment Area Study found that people suffering from one of eight medical disorders had a 41% increase in the risk of having any recent psychiatric disorder (anxiety, affective, substance abuse disorders) compared with people without chronic medical disorders. Murphy (1982) demonstrated in a sample of nondepressed elderly living in the community that the most frequent, stressful life event that was associated with a new onset of major depression was either the development of a life-threatening medical illness in the respondent or in his or her spouse. Ormel et al (2002) have shown in a longitudinal study of community elderly that there is a higher risk for developing major depression when medical illness causes a new decrement in function.

Studies of patients with specific illnesses, such as myocardial infarction, diabetes mellitus, human immunodeficiency virus (HIV)-related illness, cancer, cerebrovascular accident, and Parkinson's disease have found higher rates of major depression than in patients without these disorders. Given the extensive epidemiologic research in patients with these illnesses, I will selectively review this research, presenting meta-analyses when these have been completed. A recent meta-analysis of studies of major depression in patients with diabetes found 20 case-controlled studies of patients with and without diabetes. In these studies, the odds of major depression in the diabetes group was twice that of the nondiabetic group (odds ratio = 2.0, 95% confidence interval, 1.8-2.2) (Anderson et al 2001). Based on studies that used structured psychiatric interviews, 11%–15% of diabetics were found to meet criteria for major depressive disorder (Anderson et al 2001). Among patients with coronary artery disease hospitalized for work-up of chest pain or for those with a recent myocardial infarction, the rates of major depression have been found to be between 15% and 23% (Carney et al 1987; Frasure-Smith et al 1993; Gonzalez et al 1996; Mayou et al 2000; Schleifer et al 1989). A meta-analysis of studies of patients with HIV infection found that although prevalence rates varied between 4% and 23%, patients with HIV infection had an almost twofold higher rate of major depression than did control subjects (Ciesla and Roberts 2001).

Patients with neurologic illnesses have also been found to have a markedly higher prevalence of major depression compared with other populations. A recent article summarized the results of 14 studies that used structured psychiatric interviews to study the prevalence of major depression after stroke. The prevalence of major depression was 9%–31% in patients in the 3–4 months after stroke (Whyte and Mulsant 2002). The prevalence of major depression has been found to be 20%–30% in patients with Parkinson's disease (Mayeux et al 1984; Schrag et al 2001; Starkstein et al 1990) and 16%–30% in patients with multiple sclerosis (Hakim et al 2000; Patten et al 2000). These neurologic illnesses are likely to have direct effects on neural circuits involved in mood regulation (Whyte and Mulsant 2002). Moreover, ischemic brain disease may be important in the development of stroke, dementia, and major depression in aging populations (Thomas et al 2002).

The increased prevalence of major depression among patients with diabetes and coronary artery disease and other medical illnesses is probably due to multiple causes, including the following: 1) depression is a risk factor for the development of some specific diseases; 2) depression is a secondary psychological reaction to the development of the disease; 3) depression is secondary to the complications or aversive symptoms of that disease; 4) depression is secondary to the side effects from medication used to treat these illnesses; or 5) the chronic medical illness has a direct pathophysiologic effect on the brain (i.e., stroke, or multiple sclerosis) or has indirect physiologic effects (i.e., increasing cytokine levels or other inflammatory factors that affect the brain) (Konsman et al 2002).

Two studies have found that a history of major depression raises one's risk of development of type 2 diabetes twofold over one's lifetime (Eaton et al 1996; Kawakami et al 1999). Similarly, a recent meta-analysis of major depression as a predictor for development of coronary artery disease found an overall relative risk for development of heart disease in depressed subjects of 1.64 (95% CI, 1.29-2.08) over 11 studies (Rugulies 2002).

Conceptual Model

Figure 1 describes a conceptual model for the complex interactions between risk factors for major depression, major depression, and chronic medical illness. This model describes three known risk factors for the development of major depression: genetic vulnerability, childhood adversity, and stressful life events (Kendler et al 2002). This model also shows that an underlying vulnerability to major depression from childhood adversity (neglect and abuse experiences) may also lead to maladaptive attachment (Bifulco et al 2002a, 2002b), which may result in social isolation and difficulty collaborating with physicians (Ciechanowski et al 2001). Both childhood adversity and major depression are also associated with biobehavioral risk factors for medical illnesses, such as obesity, sedentary lifestyle, and smoking. Major depression is associated with increased symptom burden and decreased functioning and quality of life. The aversive symptoms and functional impairments associated with medical illness as well as the indirect pathophysiologic effects that these illnesses have on the brain (via increased cytokine levels or other inflammatory factors) may also cause major depression. The adverse impact of depression on patients' collabora-

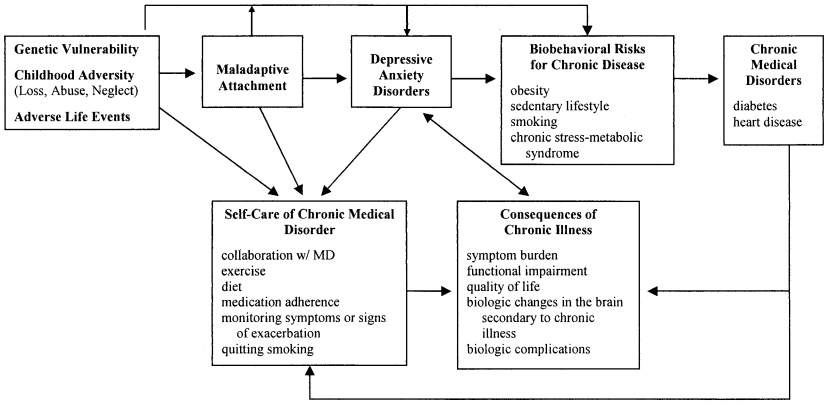

Figure 1. A conceptual model of interaction between major depression and medical illness.

tion with their physician, rate of access to preventive medical care (Druss et al 2002), and adherence to self-care regimens, in addition to depression's direct pathophysiologic effects, may increase morbidity and mortality in patients with major depression and chronic medical illness. Social and environmental support and access to quality mental health care may help buffer the effects of these risk factors (Wilkinson 2000).

Relationship of Depression to Adverse Health Behaviors and Lack of Adherence to Self-Care Regimens

Several studies have reported that patients with major depression have higher rates of adverse health-risk behaviors, such as sedentary lifestyle, smoking, and over-eating, which may lead to a higher incidence of diabetes and heart disease (Goodman and Whitaker 2002; Rosal et al 2001). Several large longitudinal studies have shown that adolescents with depression were found to have increased risk of developing obesity in their early twenties compared with adolescents without depression (Goodman and Whitaker 2002; Richardson et al, in press). In a large, prospective study, depression and anxiety were also found to be risk factors for adolescents to initiate smoking through an increased susceptibility to peer smoking (Patton et al 1998). Community adult respondents with major depression were shown in the Epidemiologic Catchment Area Study to have a significantly higher rate of smoking compared with nondepressed respondents (Glassman et al 1990).

Most medical illnesses require a variety of self-management behaviors to optimize treatment. The management of chronic medical disorders often includes collaboration with one's physician, changing one's diet, increasing exercise, taking medications regularly, and self-monitoring activities, such as checking blood glucose regularly, as well as decreasing potentially harmful behaviors, such as smoking and drinking. Depression has been shown to adversely impact self-management in many illnesses. A recent meta-analysis by Dimatteo et al (2000) showed that, compared with nondepressed medically ill patients, the odds were three times greater that medically ill patients with major depression would be nonadherent to medical treatment recommendations. In patients with diabetes, Ciechanowski et al (2000) demonstrated that depressive symptoms were associated with decreased adherence to diet and more lapses in refills of oral hypoglycemic medications. In patients with heart disease, Carney et al (1995) have shown that major depression is associated with lapses in taking daily aspirin. In patients with either stroke (Morris et al 1992) or heart disease (Blumenthal et al 1982), major depression has been shown to contribute to lack of adherence and/or drop-out from exercise rehabilitation. Recent data from patients with HIV have shown that depression also predicts lack of adherence to highly active antiretroviral therapy (HAART) (Rieera et al 2002; Spire et al 2002; van Servellen et al 2002), as well as being less likely to be treated with HAART by physicians (Cook et al 2002; Sambamoorthi et al 2000).

A study by Anda et al (1990) reported that depression symptoms significantly reduced the likelihood of quitting smoking over a 9-year period. This difficulty of quitting smoking in patients with depression may be due to the emergence of affective symptoms when patients with depression try to quit smoking. Patients with a history of major depression have been shown to be at higher risk to develop a major depressive episode when they attempt to quit smoking than patients without a history of depression (Dierker et al 2002).

Relationship of Depression to Physical Symptom Perception

Patients with both DSM-IV depressive and anxiety disorders have been found to have significantly more medically

unexplained symptoms compared with patients without these disorders when controlling for severity of medical illness (Katon et al 2001). In the Epidemiologic Catchment Area Study, 50% of community respondents with five or more medically unexplained symptoms over a 6-month period met the criteria for a DSM-III psychiatric disorder compared with 5% of respondents without these symptoms (Simon and Von Korff 1991). Kroenke et al (1994) have shown in a study of 1000 primary-care patients that as the number of medical symptoms increased, so did the percentage of patients who met the criteria for DSM-III anxiety or depressive disorders.

In patients with well-defined, chronic medical illnesses (e.g., head injury [Fann et al 1995], inflammatory bowel disease [Walker et al 1996], hepatitis C [Dwight et al 2000], diabetes mellitus [Ciechanowski et al, in press; Lustman et al 1988], chronic tinnitus with hearing impairment [Sullivan et al 1988]), studies have shown that patients with comorbid anxiety and depressive disorder had significantly more medically unexplained symptoms without identified pathology than do those with chronic medical illness alone, even after adjustment for severity of illness. Many patients with chronic illness must learn to adapt and habituate to chronic aversive symptoms, such as pain or fatigue. When patients are not depressed, most patients with chronic medical illness are able to adapt to their chronic aversive disease symptoms (Katon et al 1990); however, there is now extensive data to suggest that having comorbid anxiety and depressive disorders in patients with chronic medical illness interferes with this adaptation process and is associated with heightened awareness and focus on both symptoms of that physical illness as well as physical symptoms associated with other body organ systems (Katon et al 1990).

Illnesses with aversive symptoms, such as chronic pain, may be especially likely to provoke depressive disorder. Gureje et al (2001) showed in a multisite study of 3197 primary care patients that persistent pain at baseline predicted the onset of a psychological disorder at 12 months with the same strength that baseline psychological disorder predicted development of persistent pain. In the longitudinal study by Patten (2001) in Canada, the three illnesses (chronic sinusitis, migraine headaches, and back pain) that were associated prospectively with the highest incidence of major depression were all associated with pain. A recent study of 1801 elderly recruited for a trial testing the effectiveness of a collaborative-care intervention to improve the quality of care and outcomes of major depression or dysthymia in primary care found that more than 50% of elderly patients with affective illnesses suffered from chronic pain that was causing functional impairment and was predominately due to osteoarthritis (Unützer et al 2001).

Lustman et al (1988) have described in patients with diabetes that depressive symptoms were significantly correlated with 9 to 11 symptoms traditionally associated with poor glucose control (e.g., polyuria, polydypsia), whereas a physiologic measure of glycemic control, hemoglobin A_1C, was poorly correlated with these symptoms. This finding was recently replicated by Ciechanowski et al (in press), who found that diabetics with depression compared with diabetics without affective illness were significantly more likely to have eight of nine symptoms often associated with diabetes, when controlling for severity of diabetes. Dwight et al (2000) reported that patients with hepatitis C and higher depressive symptom severity complained of significantly more impairment from the symptom of fatigue (which is the main symptom associated with hepatitis C) compared with less-depressed hepatitis C patients, when controlling for severity of liver pathologic changes. Walker et al (1996) have shown that patients with inflammatory bowel disease and comorbid anxiety or depressive disorders complained of both significantly more gastrointestinal symptoms as well as medical symptoms in other organ systems when compared with patients with inflammatory bowel disease who did not suffer from psychiatric disorders, when controlling for severity of inflammatory bowel disease. Sullivan et al (2000) have also shown in a prospective study that in patients with coronary artery disease, depression and anxiety symptoms were significantly associated with more symptomatic reports of chest pain and fatigue 5 years later, even after controlling for the number of coronary vessels occluded, ejection fraction at baseline, and cardiac procedures over this period.

Functional Impairment

Data from the Medical Outcomes Study revealed that patients with major depression perceived their vocational and social functioning and general health as more impaired than patients with one of seven other medical conditions (Wells et al 1989). Moreover, when major depression was comorbid with chronic medical illness, there was additive functional impairment (Wells et al 1989). The MacArthur Foundation Midlife Development in the United States Study recently showed that having three or more medical and psychiatric comorbidities was associated with more work-loss days and cut-back days than the sum of the individual effects of each illness (Kessler et al 2001). This indirectly supports the hypothesis that comorbid anxiety and depressive disorders complicate the management and exacerbate the course of chronic physical conditions.

Cross-sectional studies in patients with heart disease (Sullivan et al 1996), chronic obstructive pulmonary disease (Felker et al 2001), inflammatory bowel disease (Walker et al 1996), diabetes (Ciechanowski et al 2000), HIV (Cook et al 2002), and cancer (Breitbart 1995; Massie and Popkin 1998) have all shown that major depression is associated with additive disability in these patients, even when controlling for severity of medical illness.

In a study of 2558 primary care patients aged 65 and older, Unützer et al (2000) found that elderly patients with clinically significant depressive symptoms compared with individuals with one of eight chronic medical illnesses had the third most decrements in quality-adjusted life years (QALYs) over the 4-year study, even after adjusting for differences in age, gender, and chronic medical disorders. In addition, Unützer et al (2000) showed that patients with chronic medical illness and comorbid depression had additive decrements in QALYs.

Functional impairment in aging patients predicts the development of major depression and, conversely, major depression and depressive symptoms have been found to be a risk factor for the progression of disability in the elderly (Bruce and Hoff 1994; Katz 1996; Prince et al 1998; Bruce et al 1994). A recent study by Wang et al (2002) tracked 2581 patients aged 65 years and older over a 3-year period and found that coronary heart disease, cerebrovascular disease, and depression each independently predicted increased rates of functional decline. Studies by Ormel et al (1993) and Von Korff et al (1992) have also shown that depressive symptoms and disability measures change synchronously over time—as depression improves, so do measures of functional impairment.

Several longitudinal studies have shown that depression and anxiety are more predictive of functional impairment over time than is severity of physical illness. For instance, Sullivan and colleagues demonstrated that symptoms of depression and anxiety at initial diagnosis of coronary artery disease by angiogram were more highly correlated with functional impairment at both 1- and 5-year follow-ups than was any physiologic measure (Sullivan et al 1997, 2000). This study controlled for the number of vessels occluded 70% or more, ejection fraction at baseline, and cardiac procedures over time (Sullivan et al 1997, 2000). Mayou et al (2000) showed that in patients with recent myocardial infarction, DSM-IV depressive and anxiety disorders predicted poor outcome at 1 year on all dimensions of quality of life. Several studies have also demonstrated that effective treatment of major depression in patients with chronic tinnitus and hearing impairment (Sullivan et al 1993), chronic obstructive lung disease (Borson et al 1992), and HIV (Elliott et al 2002) was associated with significant improvement in functioning that the patient had previously perceived as due to his or her medical illness.

Depression and the Doctor–Patient Relationship

Satisfaction with the quality of care of a patient's physician has been linked with enhanced adherence to medical regimens (Sherbourne et al 1992). Depressive disorders have been shown to be associated with decreased ratings of satisfaction with care (Webster et al 2001). Moreover, primary care effectiveness studies that tested interventions that were shown to improve major depressive outcomes showed that enhanced depressive outcomes were associated with increased satisfaction with care (Katon et al 1995, 1996).

Depression and anxiety disorders in adulthood are also associated with higher rates of having experienced childhood adversity (abuse and neglect) (Wainwright and Surtees 2002) as well as maladaptive attachment (Bifulco et al 2002a; Ciechanowski et al 2001). Maladaptive attachment behaviors may make it difficult to develop relationships with and trust people, including physicians. Ciechanowski et al (2001) showed that two types of maladaptive attachment in which people have difficulty relying on others (i.e., dismissing and fearful attachment) were associated with poorer adherence to diabetic regimens as well as higher hemoglobin A_1C levels. Ciechanowski et al (unpublished data) also recently showed that a decrease of depressive symptoms over an 8 to 9-month period was associated with a transition to more adaptive attachment behaviors. This suggests that affective illness increases maladaptive interpersonal behaviors, potentially making collaboration with the physician more difficult. This may explain why physicians rate patients with DSM-IV depressive and anxiety disorders as being more difficult patients to treat (Hahn et al 1996) and why patients with these disorders receive less adequate preventive medical care (Druss et al 2002).

Medical Utilization and Costs

Recent data from both mixed-aged (Simon et al 1995) and elderly samples of primary-care patients have found significantly higher medical costs in patients with either depressive symptoms or major depression compared with patients without depression (Callahan et al 1994; Unützer et al 1997; Katon et al, in press). This increase in costs is seen in every component of medical costs, including primary care visits, specialty visits, mental health visits, emergency room visits, pharmacy costs, laboratory and x-ray examinations, and inpatient costs (Callahan et al

1994; Katon et al, in press; Simon et al 1995; Unützer et al 1997).

Katon et al (in press) recently described the 6-month medical costs of approximately 9000 elderly who were screened for depression. In this study, both elderly patients with subclinical depressive symptoms and those with major depression and/or dysthymia had approximately 50% higher costs than elderly nondepressed control subjects after controlling for severity of medical illness (Katon et al, in press). After adjusting for chronic medical illness, Simon et al (1995) found that 6256 mixed-age primary-care health maintenance organization (HMO) patients with a diagnosis of depression had health care costs of approximately $4246 per year compared with costs of $2880 in a comparison group of 6257 patients with no depression diagnosis.

Two other studies of elderly primary-care patients found that depressed elderly patients also had significantly higher costs than nondepressed elderly patients. Callahan et al (1994) found that patients with depression had a mean total of outpatient costs of $1210 over a 9-month period, compared with $752 in a nondepressed control group after controlling for medical diagnosis. In an elderly cohort of 2588 from a large HMO, Unützer et al (1997) found that patients with depression had median medical costs over a 1-year period of $2147, compared with $1461 in nondepressed control subjects after adjustment for chronic medical illness. Unützer et al (1997) showed that at every level of increasing medical comorbidity, elderly patients had 30%–50% higher costs.

In one of the first studies measuring costs in primary-care patients with one chronic medical illness, Ciechanowski et al (2000) demonstrated that patients with diabetes mellitus with higher levels of depressive symptoms had significantly higher costs than did patients without depression. In this study, the authors divided a primary care population of 367 predominately type 2 diabetics into low-, medium-, and high-depression tertile categories based on depression scores on the Hopkin's Symptom Checklist (Derogatis et al 1974). The total cost of the high-tertile group was $3654, compared with $2653 in the medium-depression tertile and $2094 in the low-tertile group after adjusting for diabetes severity and medical comorbidity. These results were recently replicated by Egede et al (2002). They compared 825 adults with diabetes with 20,668 adults without diabetes using the 1996 Medical Expenditure Panel Survey (Agency for Health Care Research and Quality 2001). These investigators found that depressed patients with diabetes had health care expenditures that were 4.5 times higher than diabetics who were not depressed.

Sullivan et al (2002) also showed that patients with congestive heart failure and a diagnosis of depression had significantly higher medical costs over a 3-year period compared with those with congestive heart failure alone. Median annualized health care costs were $7474 in patients without depression, $11,012 in patients identified as being treated with an antidepressant prescription only, and $9550 in those being treated with an antidepressant and having a depression diagnosis recorded (Sullivan et al 2002). In adjusted analyses, these costs were 26%–29% higher in patients with some evidence of depression.

A study from a large HMO showed that a typical primary-care doctor has approximately 2000 patients in his or her panel, and 10% (or 200) of these patients were found to have significantly more medical visits and in-hospital days than the 1000 patients with the lowest utilization. More than half of these high utilizers were found to have significant psychological distress, and among the distressed high-utilizers, more than two thirds had recurrent major depressive episodes (Katon et al 1990). More than two thirds of these distressed high-utilizers also had one or more chronic medical illnesses, showing the very high rate of psychiatric and medical comorbidity in high-utilizing primary care populations (Katon et al 1990).

McFarland et al (1985) also showed in a large Oregon HMO that high-utilizing elderly patients suffer from high rates of major depression and chronic medical illness. A study by Luber et al (2001) found that elderly primary-care patients with a diagnosis of depression by their primary-care provider used significantly more primary-care appointments and medications after controlling for severity of medical illness, compared with nondepressed control subjects.

Several studies of large, inpatient medical and surgical populations have found that patients with comorbid affective illness had significantly longer lengths of stay after controlling for severity of medical illness, compared with nondepressed control subjects (Levenson et al 1990; Saravay et al 1996). In a recent study of 380 cardiac rehabilitation patients screened for depression, it was found that depression significantly increased the cardiac rehospitalization rate in these patients (Allison et al 1995).

Relationship of Depression to Mortality

Multiple large, epidemiologic studies have examined whether depressive symptoms or major depression increased the risk of mortality. A systematic survey of 57 studies (1966–1996) from the world's literature examining the risk of increased mortality in patients with depression found that 29 (51%) were positive, 13 (23%) were negative, and 15 (26%) were mixed (Wulsin et al 1999). The summary of this analysis suggested that depression seemed to increase the risk of death from cardiovascular

disease, especially in men, with future studies needed to control for multiple potential confounders, such as obesity, poor health, and smoking. A more recent systematic review examined the literature between 1997 and 2001 and found 61 reports meeting their inclusion criteria. This review found 44 studies (72%) reporting a positive association between depression and mortality and 17 (28%) reporting no association. Positive studies had a longer median length of follow-up and were more likely to use structured psychiatric interviews to define major depression rather than depression self-rating scales.

Most epidemiologic studies show that depressive symptoms as well as major depression raise the risk of developing coronary artery disease as well as dying from heart disease. The following are selected references in this extensive literature. Frasure-Smith et al (1993) reported that patients admitted to the hospital with a myocardial infarction who suffered from major depression had a fourfold increase in mortality over the next 6 months compared with people without affective illness, controlling for severity of coronary artery disease. Ferketich et al (2000) analyzed the results from 5007 women and 2886 men enrolled in the 10-year National Health and Nutrition Survey and found that depressed men had a 71% greater risk of developing heart disease and were 2.34 times more likely to die from this condition compared with nondepressed men. On the other hand, depressed women faced a 73% higher risk of development of heart disease but were not more likely to die compared with controls without depression (Ferketich et al 2000). A nationally representative survey of 8000 community Finnish respondents also showed in a 6.6-year follow-up that the risk of coronary death was increased in depressed persons both with and without cardiovascular disease at entry to the study (Aromaa et al 1994). Unützer et al (2002) found that the 3% of the sample of 2558 Medicare recipients aged 65 and older with the most severe depressive symptoms had an increased risk of mortality over a 7-year period, even after adjusting for health risk behaviors and chronic medical conditions. A recent analysis of a national cross-sectional survey of Medicare enrollees showed that a positive response to one of two questions about sadness or anhedonia was associated with a 1.3% higher risk of dying after adjusting for age, gender, and the presence of heart disease (Cooper et al 2002). Research has also shown that negative emotions, such as hostility and anger, are associated with increased mortality after myocardial infarction, even when controlling for heart disease severity (Lespérance and Frasure-Smith 1996).

Mechanisms for Increased Cardiac Risk

Recent research studies have suggested several possible biologic mechanisms that may explain why major depression increases risk after myocardial infarction. These studies have described that depressed patients had decreased heart rate variability (Gorman and Sloan 2000), increased platelet aggregation (Laghrissi-Thode et al 1997; Musselman et al 1996; Pollock et al 2000; Whyte et al 2001), higher levels of inflammatory risk markers (C-reactive protein and interleukin-6) (Miller et al 2002), and decreased adherence to lifestyle changes, such as exercising (Blumenthal et al 1982), quitting smoking (Anda et al 1990), and taking medications (Carney et al 1995).

Conclusion and Future Research Directions

The data suggest that there is a higher incidence and prevalence of major depression in patients with chronic medical illness. Major depression is associated with more health-risk behaviors such as smoking, sedentary lifestyle, and over-eating, which may increase risk of incidence of medical illness. The aversive symptoms, functional decrements, or physiologic changes associated with chronic medical illness may also increase the incidence and prevalence of major depression. Depression has been shown to be associated with increased symptom burden, increased functional impairment, decreased quality of life, and increased medical costs in patients with chronic medical illness, as well as decreased adherence to self-care regimens. Important future research directions include the following:

1. Large, prospective, epidemiologic trials are needed to measure both a priori-defined health-risk behaviors and pathophysiologic mechanisms to better understand the mechanisms by which depression increases the risk of medical illness and mortality.
2. Large-scale, prospective studies in patients with chronic medical illnesses are also needed to improve understanding of the reciprocal effects between depression, chronic medical illness, and symptom burden, functional impairment, and self-care regimens. These studies need to creatively develop testable models of reciprocal effects or potential negative synergistic effects (e.g., osteoarthritis causes function decrements causing depression, which leads to further deactivation and more functional decrements over time; Schulz et al 2002).
3. Large, randomized, controlled studies are needed in representative populations with chronic medical illness and major depression to test the effect of enhancing quality of depression care and improving outcomes of depression on symptom burden, function, self-care activities, direct and indirect costs, medical complications, and mortality.

4. Biological studies are needed to determine the adverse impact of major depression on physiologic factors that affect chronic medical illness, such as platelet activation, heart rate variability, inflammatory markers, the immunologic system, and the metabolic system.

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