Depression and the Course of Coronary Artery Disease

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Literature and folk wisdom have long linked depression and death; however, only recently have scientific studies examined the relation between them. Beginning in the 1970s, investigators compared mortality among patients treated for major depression and the general population. Nine of ten studies found an increased mortality from cardiovascular disease among depressed patients. However, such studies confound the relation between depression and its treatment. Community surveys circumvent this difficulty, but as these studies began to appear, other investigations revealed the strong association between depression and cigarette smoking, which made obvious a need to control for smoking. The first study to do this appeared in 1993, and not only did a relation between depression and mortality persist, but a relation between depression and the development of ischemic disease was revealed. In the past 2 years, six more community surveys have followed populations initially free of disease, and five have observed an increased risk of ischemic heart disease among depressed persons. Another research strategy is to start with subjects who have preexisting cardiovascular disease. Here, too, depression has consistently been associated with a worse outcome. In one well-designed study, patients with depression in the period immediately after a myocardial infarction were 3.5 times more likely to die than nondepressed patients. The basis of this association remains speculative. However, it is likely that the changes in the autonomic nervous system and platelets that are seen in depression account for a substantial portion of the association. (Am J Psychiatry 1998; 155:4-11)

For centuries poets and folklore have asserted that there is a relation between the mind and body in general and human moods and the heart in particular. Almost 400 years ago Shakespeare wrote, “My life... sinks down to death, oppress’d with melancholy” (Sonnet 43). However, only in the last few years has this conviction been scientifically tested. Nevertheless, it is now abundantly clear that depression is associated with ischemic heart disease.

PATIENTS COMPARED WITH THE GENERAL POPULATION

The first scientific effort to test this relationship was a study by Malzberg published in The American Journal of Psychiatry in 1937 (1). He compared the mortality rate of patients with involuntarily depressed in the New York State civil hospital system and the rate in the general population of the state. As hypothesized, the mortality rate for the patients was markedly elevated as it was for patients with both cardiovascular and infectious diseases. However, the study conspicuously confounded the influence of involuntary depression with that of chronic institutionalization. Although the results were dramatic, they were not convincing, and the issues involved were not further tested for almost 40 years.

To some extent this hiatus was a consequence of World War II, but beyond the war, psychiatry was focused on psychoanalysis and personality and, with respect to heart disease, type A behavior. In the mid-1970s, several investigators began to reexamine the impact of depressive diagnoses. One of the earliest and most impressive of these studies was that of Week et al. (2), who took advantage of the Danish National Registry and identified all individuals with a diagnosis of either major depression or manic-depressive disease between 1974 and 1978. All causes of natural death were examined, and there was a 50% increase in deaths from cardiovascular disease.
diovascular disease among depressed patients compared with the general Danish population. This study followed 6,000 patients for an average of 5 years, and unlike the Malzberg study group, the vast majority of the patients were not institutionalized. The Weeke data raised the concern that in the 40 years since Malzberg’s study, drug treatments (tricyclic antidepressants and lithium) had become common, and the association between death and depression could be confounded by these treatments. However, although the literature is limited, it suggests that adequate treatment—whether with tricyclics, lithium, or ECT—reduces rather than increases mortality (3–6).

Moreover, Weeke herself addressed this question in a second study (7) in which she and her associates compared the relative risk of mortality from cardiovascular disease in depressed populations before and after the introduction of antidepressant drug treatments. The relative risk of mortality was elevated in both periods, but the risk was actually lower during the era of drug treatment. This, again, tends to support the suggestion that appropriate treatment might reduce the cardiovascular risk associated with major depression.

Besides the two Weeke studies (2, 7), Tsuang et al. (8), Norton and Whalley (9), and Rabins et al. (10), using methods very similar to that of Weeke and colleagues, compared depressed patients with the general population. All three of these 1980s studies found an excess of deaths from cardiovascular disease among depressed patients. In the 1990s Sharma and Markar (11) reported an excess of deaths from cardiovascular disease in 472 manic-depressive patients over a 17-year period, while Vestergaard and Aagaard (12), in a smaller group of subjects with bipolar depression, found a very similar result. Earlier, Black et al. (13) had examined 5,412 psychiatric patients admitted to the University of Iowa Psychiatric Hospital. They found an elevated mortality risk in the female but not the male depressed patients. They did observe an elevated relative risk of mortality from cardiovascular disease for the whole sample but did not specifically examine the mortality rate from cardiovascular disease in the depressed group. In general, the findings of Black and associates, although statistically significant and in the same direction as those of the other seven studies, were not as dramatic.

The one study with negative results that compared patients with the general population used the Central Psychiatric Case Register of Israel. The observations of Zilber and colleagues (14) were based on a 5-year follow-up of depressed patients that involved 7,868 person-years. Total mortality was significantly elevated, but unlike others, Zilber et al. found that the bulk of this excess was due to infection rather than cardiovascular disease. They pointed out that a major difference between their data and that of others is that they studied patients admitted to psychiatric hospitals rather than to psychiatric services of general medical hospitals. This process would have limited their sample to very severe and refractory cases of affective disorder, but it is not clear why this should reduce the association with cardiovascular disease.

STUDY OF COMMUNITY VERSUS CLINICAL POPULATIONS

Examining community epidemiological samples rather than study groups based on patients seeking treatment circumvents both the influence of institutionalization and any potential effect of treatment. In this situation the vast majority of cases of depression that are identified involve persons who have never had any antidepressant treatment. Using community-based samples also significantly shifts the focus from more severe to less severe cases. It would be easy to think that the phenomena responsible for the increased mortality seen in treatment samples would not be strong enough to manifest an effect in milder cases. Nevertheless, two studies based on community samples demonstrated a significant association between depression and mortality. Murphy et al. (15) used the data from 1,000 individuals who were followed for 16 years in Sterling County, Canada, and Bruce et al. (16) examined the data from 3,500 individuals followed for 9 years in New Haven, Conn. Murphy et al. investigated cause of death, and depression was explicitly associated with mortality from cardiovascular disease. The investigators in the New Haven study did not give information about cause beyond saying that the excess deaths were due to natural causes.

THE CONFOUNDING EFFECT OF CARDIAC RISK FACTORS

For more than 20 years, a major focus of our research group has been the cardiovascular effects of the various antidepressant drugs, and we have followed quite closely the possibility that depression itself could influence cardiovascular disease. By the late 1980s, it was the opinion of the first author (A.H.G.) that the evidence linking depression and mortality due to cardiac disease had become quite convincing. During that same period, another aspect of our work involved nicotine and resulted in the observation that the mere history of major depression, even in the absence of current illness, increased the likelihood that a person would smoke and, if that person attempted to quit, increased the chances that he or she would fail (17). When we began to study nicotine, it did not occur to us that smoking studies would be connected to our interest in depression and cardiovascular disease. However, even before the first replication was published, it was apparent that the association between depression and smoking represented a potentially serious confounding factor in the relation between depression and mortality. The relationship could simply be that depressed individuals were more likely to smoke and that smoking caused cardiovascular disease.
DEPRESSION AND CORONARY ARTERY DISEASE

One of the earliest replications of our original observation came from the Centers for Disease Control (CDC). Using the National Health and Nutrition Epidemiological Study data, Anda et al. (18) found almost exactly what we had found using data from St. Louis (19). While discussing the differences in our data sets, Anda et al. described another CDC data set called the Medical Illness Follow-Up Study. We quickly realized that this data set contained not only information about depression and smoking but also information about depression and death, while controlling for smoking (20). Information was available on 2,382 individuals over the age of 45 years who were found to be free of any disease after a physical examination and laboratory tests were then followed for 12½ years. To preclude the possibility that subjects had some awareness that they were ill which was not revealed by their history, laboratory tests, or physical examination, patients who developed their illness in the first 2½ years of the study were excluded. Nevertheless, after controlling for smoking and other known risk factors for cardiovascular disease (gender, weight, activity, blood pressure, and cholesterol), we found that the apparently healthy individuals who had elevated depression ratings were more likely both to develop and to die of ischemic heart disease. Even after separation of the sample into those who smoked and those who did not, the influence of depression persisted. In addition to the control for smoking, this is the first study to link depression with the dual risk of both developing and dying of ischemic heart disease.

In the last few years, six more epidemiological studies (21–26) have taken a similar approach to different data sets. All of these studies controlled for smoking, and five of the six studies found a relation between depression and cardiovascular disease. Ford et al. (26) reported on 1,198 male former Johns Hopkins University medical students followed for a median of 35 years. The men with depression had a higher relative risk of myocardial infarction (relative risk = 1.68, 95% confidence interval = 1.03–2.74) than the men free of depression. On average, the first report of depression preceded the first report of cardiovascular disease by 10 years. Aronma et al. (21) reported on the Mini-Finland Health Survey follow-up of individuals 40–64 years of age. The study was based on 5,555 persons who had both medical and psychiatric evaluations at baseline and were followed an average of 6.6 years. The risks of developing and of dying of ischemic heart disease were both significantly elevated among depressed individuals after control for age, education, and traditional ischemic heart disease risk factors including smoking.

The Kuopio Ischemic Heart Disease Study (22) followed a separate sample of 2,428 Finnish men over a 6-year period. In this study, very much like the findings of Anda et al. in the United States, men without any prior history of angina or myocardial infarction who had higher levels of depression were more likely to experience a first infarction, even after control for a wide array of biological, behavioral, and social risk factors.

There was again an elevated risk of mortality from cardiovascular disease among the men with higher depression scores.

Another recently published long-term study that controlled for smoking is that of the Glostrup cohort (23). This was a study of 730 persons born in Glostrup, Denmark, in 1915. They had both physical and psychological examinations in 1964 and again in 1974 and were followed an average of 27 years. After control for both smoking and physical health, the investigators found, as with the CDC and Finnish data, that individuals with elevated depression scores were 63% more likely to develop ischemic heart disease. Elevated depression scores were also associated with a significant increase in all natural causes of death; however, the investigators did not address the question of whether increased mortality rate was specifically due to cardiovascular disease.

The most recently published data come from a year follow-up of the Baltimore cohort of the Epidemiologic Catchment Area study (24). Among the 1,551 respondents who were apparently free of medical illness at baseline, a diagnosis of major depression increased the risk of myocardial infarction more than fourfold after control for both medical risk factors and psychiatric diagnoses. This study is interesting because it used a DSM-III diagnosis of depression, it is the only study to control for other psychiatric diagnoses, and it included the category of dysphoria in the same population. Individuals who were dysphoric but never met lifetime criteria for major depression were intermediate in their risk for myocardial infarction compared with those with DSM-III major depression and those who were totally free of depression.

Only one study that started with healthy individuals and controlled for all of the usual medical risk factors failed to find a relation between depression and ischemic heart disease and/or mortality due to cardiovascular disease. That study was the 15-year follow-up of 2,573 members of the Northwest Region of Kaiser Permanente (25). Only 1,399 of these persons were over the age of 45 years. Even in this study the authors referred to a "possible" relation between mortality and depression among men.

EXAMINING CARDIAC PATIENTS RATHER THAN HEALTHY INDIVIDUALS

In 1988 Carney et al. (27) used a study strategy that started with patients who already had cardiovascular disease. They conducted structured psychiatric examinations of consecutive patients undergoing coronary angiography. Of the 32 patients whose studies confirmed the presence of coronary artery disease, just 10% met criteria for major depression. This depressed group turned out to be about 2½ times more likely to develop a serious adverse cardiac complication over the next 12 months. Although the study group was too small to control adequately for other risk factors,
this was corrected in subsequent studies using the same strategy.

Ahern and colleagues (28) obtained baseline ratings of anxiety, anger, and depression in 330 patients with ventricular arrhythmia following a heart attack. The postinfarction patients who survived the first year had lower baseline depression scores than the nonsurvivors after the usual medical and social risk factors were controlled. Neither anger nor anxiety scores were associated with survival. Several other investigators studying post-myocardial-infarction patients have also found a higher mortality associated with depression (29–32). The most convincing of these studies was the one by Frasure-Smith et al. in 1993 (32).

Frasure-Smith and colleagues obtained structured psychiatric examinations of 222 patients 5–15 days after they suffered myocardial infarction. The patients were contacted again 6, 12, and 18 months after discharge from the hospital. Sixteen percent of these patients showed evidence of major depression while hospitalized for their index myocardial infarction. This is consistent with the other surveys that regularly show 15%–20% of postinfarction patients developing major depression (33, 34). At 6 months approximately 17% of the depressed patients in the study by Frasure-Smith et al. (32) had died, compared with 3% of the nondepressed patients. With control for other independent predictors of risk, the relative hazard for the depressed patients was almost 3.5 times greater than for the nondepressed patients. The strongest medical predictors of mortality after myocardial infarction is generally heart failure, and it is associated with just about the same 3.5-fold increase in mortality.

Although concern has regularly been expressed about the reliability of a diagnosis of depression made in a medically ill patient, and especially a post-myocardial-infarction patient, only 25% of the patients Frasure-Smith et al. identified as depressed were free of major depression at both the 6- and 12-month follow-up interviews (35). This compares with 81% of those who did not originally receive a diagnosis of depression who remained free of depression. Similarly, Hance et al. (34) found that one-half of patients diagnosed as having major depression in the immediate postinfarction period either remained depressed or relapsed within 12 months.

In addition to studying patients with the diagnosis of major depression, Frasure-Smith et al. also measured symptoms of depression with the Beck Depression Inventory (36). Six months after myocardial infarction, the patients who had elevated Beck inventory scores but were free of major depression had mortality rates much like those of the patients who were free of any depression. However, by 12 months, the patients with Beck inventory scores above 10 were dying at a rate significantly higher than that of the patients without depression, and by 18 months their mortality rate was not much less than that of the patients with major depression (37). It is not clear whether this increased mortality was really associated with lesser degrees of depression or whether these high Beck inventory scores were merely identifying a group at high risk for major depression. In the Hance et al. study (34), 42% of patients with minor depression developed major depression over the subsequent 12 months.

Recently, Barefoot and his co-workers at Duke University (38) published a 17-year follow-up of patients admitted to the cardiology service with a diagnosis of coronary artery disease. This study combined the strategies of using a high-risk population and using a long-term follow-up. Once again, depression was associated with diminished survival among patients with preexisting cardiovascular disease.

Taken together, these studies constitute a convincing body of evidence linking depression, cardiovascular disease, and mortality. Moreover, this relationship seems to have at least two components. All six of the studies that specifically examined patients with preexisting cardiovascular disease found higher mortality rates over the next 6–12 months among the depressed patients than among the nondepressed patients. These studies were well controlled for both medical and social risk factors, and the evidence is particularly strong in the postinfarction patients. The second component involves the relative risk of experiencing a first heart attack among persons initially free of heart disease. Here again, the evidence is strong and generally well controlled. Six of the seven studies that identified healthy individuals at baseline, controlled for cardiovascular risk factors including smoking, and recorded new episodes of cardiovascular morbidity found a significantly elevated risk among the persons who had higher depression scores at baseline (20–24, 26). That increased risk of morbidity is generally from 1.5 to 2.0 times and is about one-half the magnitude of the increase in mortality that depression confers in post-myocardial-infarction patients.

OTHER ISSUES

Although there is no question that depression is associated with both developing cardiovascular disease and death, there are a number of issues that remain to be clarified. One is whether the association with cardiovascular disease and death is unique to depression or whether it exists with other negative mood states. The next best body of information concerns anxiety, but it is neither as extensive nor as sophisticated as the literature on depression. It is beyond the scope of this article to examine these data in detail, but it is our opinion that they suggest that phobic anxiety or panic states are associated with death, most clearly sudden death, over the long term (39, 40). However, unlike depression, higher levels of general anxiety in initially healthy individuals do not seem to be associated with an increased rate of developing or dying of cardiovascular disease (39–42). If there is a short-term effect of anxiety on mortality from cardiovascular disease, it is not as robust or as easy to demonstrate as that of depression (28, 43, 44).

Another unresolved issue is precisely what it is that