Depression and Heart Disease

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Heart disease, and particularly coronary artery disease, remains the most common cause of death in the United States, with over one half million new myocardial infarctions reported annually. Depression is common in heart disease patients, and recent evidence strongly supports the view that it increases the risk of development, clinical progression, and fatal complications of coronary artery disease.\textsuperscript{1,13} Depression in heart disease patients has been shown to be persistent\textsuperscript{14} and is associated with impairment in social and occupational function after myocardial infarction beyond that attributable to heart disease alone.\textsuperscript{15} For these reasons, defining the optimum treatment of depression in the patient with heart disease is a matter of urgency. Recent developments in psychopharmacology have altered our views of available pharmacotherapies. These developments include revised estimates of the risks associated with tricyclic antidepressants in ischemic heart disease patients,\textsuperscript{15} the emergence of data on cardiovascular effects of serotonergic antidepressants,\textsuperscript{16,17} studies of serotonergic agents in ischemic heart disease patients,\textsuperscript{18-20} exploration of the role of serotonergic agents in attenuating anger and aggression,\textsuperscript{21-26} and, most recently, a growing appreciation of the interrelationships among depression, platelet function, ischemic heart disease events, and serotonergic antidepressant drugs.\textsuperscript{27-30} The goal of this article is to review these developments and provide the clinician with an appreciation of the issues in selecting treatment for depressed patients with heart disease.

THE RELATIONSHIP BETWEEN DEPRESSION AND THE INCIDENCE AND PROGRESSION OF CORONARY ARTERY DISEASE

Evidence of a relationship between depression and heart disease is derived from four groups of studies: observations of psychiatric patient samples, community epidemiologic studies without control for cardiac risk factors, epidemiologic studies that do control for cardiac risk factors (including smoking), and follow-up of heart disease patient samples. An excess of cardiovascular mortality was demonstrated in studies of depressed psychiatric patients beginning in the 1930s.\textsuperscript{1,30-35} These studies were of limited value because they used hospitalized sample populations in which many confounding variables may have existed. These studies were therefore succeeded by community sample studies. The Stinson County Study\textsuperscript{2} and follow-up of subjects from the New Haven node of the Epidemiological Catchment Area study\textsuperscript{3} also demonstrated a relationship between depression and subsequent cardiovascular mortality. When evidence emerged in the 1980s that depression in the community and in patient samples is associated with a higher prevalence of smoking and lower successful quit rates, the need to control for smoking in studies of depression and heart disease became clear.\textsuperscript{36,34} Anda and colleagues\textsuperscript{4} used a large prospectively collected cohort to resolve this

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issue. They studied a group of 2832 American adults over age 45 with no baseline ischemic heart disease or other medical problems at baseline, and mean follow up of 12.4 years. Controlling for medical variables, education, marital status, physical activity, and smoking, and after excluding mortality in the first 2 years, symptoms of depression at baseline were associated with an approximately 50% to 60% increased risk of fatal and nonfatal heart disease. The increased risk associated with depression was found in both smokers and non-smokers. Subsequently, data from a large Danish cohort with a 27-year follow up have supported this finding. Depressive symptoms were associated with a 1.7-fold increased risk of acute myocardial infarction and 1.59-fold increased total mortality. Again, the findings held for both smokers and non-smokers. A recent study of hopelessness in a Finnish cohort of 2428 middle-aged men also demonstrated a relationship between hopelessness and both first myocardial infarction and cardiovascular mortality, as well as total mortality, after adjusting for other risk factors, including smoking. The last approach to establishing the importance of depression in heart disease has been the examination of heart disease patients. In a small but very suggestive study, Carney and Freedland followed a cohort of 52 patients with newly diagnosed coronary artery disease who were given structured interviews for psychiatric diagnosis at the time of diagnostic coronary angiography. Nine of the 52 patients met criteria for major depressive disorder. The depressed and non-depressed patients were well matched with respect to disease severity and other risk factors, except for smoking, which was more common in the depressed group. Depressed patients were approximately twice as likely to experience myocardial infarction, need for coronary revascularization, and death over the next 12 months. Depression occurs in approximately 20% of post-myocardial infarction patients. In a post-myocardial infarction sample, depressive symptoms were associated with increased 1-year mortality in a trial of antiarrhythmic drug therapy for patients with frequent premature ventricular contractions. Anxiety and depression ratings were associated with 5-year cardiac mortality in a naturalistic follow-up study limited to men. Ladwig used multivariate analyses to examine the effects of depression in 560 male survivors of acute myocardial infarction, and found that major depressive disorder was marginally related to mortality, whereas increasing severity of depressive symptoms was significantly correlated with risk of death, after adjustment for other prognostic factors.

The most comprehensive study on post-myocardial depression is that of Frazer-Smith and Lesperance, who obtained structured psychiatric interviews and psychological rating scales in 222 patients approximately 10 days after hospitalization for acute myocardial infarction. The sample included men and women. In the 35 patients (16%) who met criteria for current major depressive disorder, there was an approximately fourfold increased mortality at 6 months as compared with the non-depressed group, even after adjustment for other prognostic factors in a multivariate regression analysis. At 18 months follow up, an elevated score on the Beck Depression Inventory at the time of initial assessment was associated with an eightfold increase in mortality. The combination of elevated Beck Depression Inventory scores and frequent premature ventricular contractions after the index infarction was the best predictor of subsequent death in the 18-month follow up. Most of the deaths were sudden cardiac deaths, suggesting that depression increases the risk for malignant arrhythmias in post-myocardial infarction patients.

Consistent with this hypothesis are observations that depression is associated with alterations of autonomic nervous system control of the heart. Studies to date suggest a reduction of parasympathetic modulation of heart rate, as measured through assessment of heart period variability. Such autonomic dysfunction has been identified as a negative prognostic factor in other studies of post-myocardial infarction risk stratification. However, other plausible mechanisms may underlie the association of depression and mortality. A psychological mechanism, namely, that depressed patients are less likely to adhere to treatment plans that result in improved outcome, is plausible, but there are few data available to test its effect.

Finally, two recent studies suggest that increased tendency to thrombosis may occur in depression. In one study, patients with depression and ischemic heart disease were shown to have higher levels of circulating platelet factor 4 and beta-thromboglobulin, markers of platelet activation, than either non-depressed ischemic heart disease patients or normal control subjects. This abnormality was reversed by treatment with the serotonergic antidepressant paroxetine, but not by nortriptyline. In the second study, medication-free, otherwise healthy patients with major depression had increased procoagulant function at baseline and exaggerated platelet reactivity to orthostatic challenge compared with normal comparison subjects. In recent years, prevailing views of the pathogenesis of acute coronary syndromes have come to emphasize the importance of thrombus formation superimposed on preexisting intracoronary atherosclerotic plaque. Plaque formation is a chronic process with stabilization of plaque associated with development of a fibrous cap over its lipid, calcium, and cellular matrix. Damage to the fibrous cap ("ulceration" or "rupture" of the plaque) exposes thrombogenic lipid material, which stimulates platelet activation and aggregation, thrombus formation, and arterial occlusion. Attempts to interfere with clot

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formation and promote rapid lysis of already formed clots have shown to be a major thrust of recent research in acute coronary syndromes.\textsuperscript{52,53} It is of interest, therefore, that serotonin reuptake inhibitors have the effect of depleting platelet serotonin stores, which are an integral requirement for platelet aggregation. The possibility that antidepressant treatment might interfere with the formation of thrombus on ruptured plaque suggests that these agents might have a beneficial effect on the risk of ischemic events in patients with coronary disease. Although these studies are in an early stage, they suggest a possible role for serotonin agents in reducing thrombotic events in coronary disease patients with depression.

**PHARMACOTHERAPY CONSIDERATIONS IN TREATMENT OF DEPRESSED PATIENTS WITH HEART DISEASE**

The findings discussed above have heightened interest in establishing safe and effective therapy for depression in heart disease patients. The tricyclic antidepressants have been extensively studied in patients with cardiovascular disease. In addition to their anticholinergic and sedative side effects, their cardiovascular side effects include atrioventricular node and intraventricular conduction delay, bundle branch block, complete heart block, and orthostatic hypotension.\textsuperscript{44,45} In patients with pre-existing impairment of left ventricular function, imipramine causes a substantial incidence of symptomatic orthostatic hypotension, with falls and fractures occurring as complications. However, nortriptyline appears to be well tolerated by most patients when adjusted to therapeutic blood levels.\textsuperscript{46} Although toxicity of tricyclic antidepressants may manifest with ventricular tachyarrhythmias, at therapeutic blood levels, tricyclic antidepressants have a quinidine-like (type 1A) antiarrhythmic effect.\textsuperscript{47,48} In theory, therefore, a tricyclic antidepressant might be used to treat the patient with myocardial infarction, ventricular arrhythmias, and depression. However, the Cardiac Arrhythmia Suppression Trial, a test of the efficacy of antiarrhythmic agents in preventing sudden cardiac death in patients with recent myocardial infarction and frequent ventricular premature depolarizations, established that type 1 antiarrhythmic agents actually increase mortality compared with placebo treatment.\textsuperscript{49-51} This is an effect specifically confirmed in a meta-analysis of the effects of quinidine,\textsuperscript{52} and appears to be mediated by ischemia.\textsuperscript{53} Consequently, use of alternatives to tricyclic antidepressants should be considered for ischemic heart disease patients.\textsuperscript{15}

Serotoninergic antidepressants have generally come to be viewed as first-line treatment for most cases of depression. In contrast to tricyclic agents, the serotonin reuptake inhibitors appear to have minimal cardiovascular effects in subjects free of heart disease.\textsuperscript{54,55} They do not affect cardiac conduction or blood pressure. Slowing of heart rate by 2 to 3 beats per minute is common but generally of no clinical significance. Rare cases of symptomatic bradycardia have been reported in association with use of serotoninergic agents.\textsuperscript{54,55} In addition to their cardiovascular effects, effects on bleeding and coagulation are germane to an appreciation of the role of serotoninergic antidepressants in treatment of heart disease patients. In anecdotical reports, increased bleeding has been associated with fluoxetine and paroxetine.\textsuperscript{56,57} The few systematic studies of bleeding and coagulation in serotonin reuptake inhibitor—treated patients, however, generally do not find a clear relationship of drug treatment with changes in coagulation parameters. Berk and colleagues\textsuperscript{56} examined the effects of fluoxetine on bleeding and coagulation. They studied 13 patients with major depression before and 1 month after initiation of fluoxetine. Patients with a history of coagulation abnormalities with significant medical problems or taking aspirin or anticoagulants were excluded. Ten patients completed the trial. There were no effects of treatment on prothrombin time or its normalized ratio (INR), partial thromboplastin time, platelet count, clotting factors, fibrinogen, thrombin time, bleeding time, euglobulin lysis time, protein kinase C, antithrombin, D dimer latex, lupus inhibitor, or platelet activation by epinephrine, adenosine diphosphate, or collagen. One patient subsequently received paroxetine and developed a petechial rash, which resolved after paroxetine discontinuation. Elevated international normalized ratio values were reported in a series of patients undergoing cardiac rehabilitation who received treatment with a variety of serotoninergic antidepressants along with warfarin, suggesting an effect on warfarin metabolism.\textsuperscript{57} In view of the relationships between platelet activation, depression, and heart disease, the effects of serotonin reuptake inhibitors may actually be of potential value.

Few studies have examined the use of serotonin reuptake inhibitors in patients with heart disease. Roeser and colleagues\textsuperscript{58} examined the effect of fluoxetine in a group of 22 hospitalized, severely depressed, older patients with stable heart disease. Although the cardiac diagnoses were heterogeneous, a majority of the patients had atherosclerotic coronary artery disease, and most patients had mild to moderate impairment of left ventricular function. These patients received 6 weeks of fluoxetine therapy, with the final 3 weeks at 60 mg/day. Cardiovascular effects observed included no effect on blood pressure, no orthostatic hypotension, a 2- to 3-beat per minute slowing of heart rate, which was of no clinical significance in any case, no effect on ventricular premature contractions, no effect on cardiac conduction, and, unexpectedly, a modest but significant increase in left ventricular ejection fraction. Compared with a historical control group of patients treated with nortriptyline, the adverse event rate was lower (24% versus 22 patients dropping out. However, the efficacy of fluoxetine in this study was disap.
pointing; only 23% of patients starting fluoxetine achieved substantial improvement, compared with 67% in the nortriptyline-treated comparison group. For melancholic patients, fluoxetine achieved only a 10% response rate.

In another randomized study, Roose and colleagues compared paroxetine and nortriptyline in a similar group of older depressed patients with ischemic heart disease. Ninety percent of paroxetine-treated patients completed the trial, and 68% responded to the medication. In contrast, only 68% of nortriptyline-treated patients completed the trial, but 85% were judged responders. The cardiovascular effects of paroxetine were minimal.

After Frasure-Smith and Lesperance found that depression in the period immediately after myocardial infarction is associated with greatly heightened mortality over the next 6 to 18 months, interest in possible intervention for this patient group has grown. Can such patients be treated safely and effectively with antidepressants? Would such treatment improve their survival? The first study aimed at addressing this problem was a multiple-site, open-label, pilot study of sertraline treatment for patients found to meet criteria for major depressive disorder at screening 5 to 30 days after myocardial infarction. Twenty-six patients received 50 to 200 mg/day of sertraline in a 16-week protocol. Substantial improvement in depressive symptoms was demonstrated with Hamilton and Beck depression ratings and with the Clinical Global Improvement scale. As in the fluoxetine and paroxetine studies, the hemodynamic, electrocardiographic, and antiarrhythmic effects of the drug were minimal. Three patients withdrew from the study because of adverse events; none of these was a cardiovascular complication. However, cardiovascular events did occur, including unstable angina and reinfarction. Whether these events can be attributed to sertraline treatment cannot be ascertained through the open-label study design employed, because such events can be expected to occur in the natural history of patients with myocardial infarction. A controlled trial is needed.

Two recently initiated studies will attempt to respond to this need. The ENRICHED Trial, sponsored by the National Heart, Lung, and Blood Institute, is a multicenter trial of combined psychosocial and pharmacologic interventions for patients with depression and social isolation after myocardial infarction. A randomized, placebo-controlled trial of sertraline in post-myocardial infarction depression is also in its early stages.

Another possible role for use of serotonergic agents in heart disease is in the treatment of anger or aggression. Hostility has been associated with increased incidence of coronary artery disease, possibly due to altered autonomic cardiovascular control and exaggerated physiologic reactivity to psychological stress.

Exaggerated reactivity in turn has been associated with increased development of coronary artery plaque in animals and with recurrent cardiac events in patients with known coronary disease reformat. Since Aasberg described a relationship between violence and low central nervous system serotonergic function in suicidal patients, a number of investigators have found evidence of low serotonergic function in a variety of "aggressive" populations.

Numerous small trials of serotonergic agents for reduction of anger, hostility, or aggression have been reported. Most of these trials have been conducted in patients with depression, anger attacks, or borderline personality disorder, and although the results are not entirely consistent, they tend to show reduction in some measures of anger or aggression. To apply this line of research to patients with heart disease, Littman conducted an 8-week open trial of buspirone, a direct 5HT2 serotonin receptor agonist, in 10 men with Type A Behavior Pattern, coronary artery disease, and "irritability," but no Axis I psychiatric disorder. The mean final dose of buspirone was 42 mg/day. Buspirone treatment was associated with significant reduction of total symptoms, anxiety, and some but not all measures employed to rate hostility, and on Type A Behavior Pattern total score. Further research is necessary to indicate if serotonergic treatment can reduce anger or reactivity or coronary events related to these patient characteristics.

Potential drug-drug interactions via effects on hepatic metabolism should be recognized when using antidepressants in heart disease patients. An exhaustive review is beyond the scope of this article but is available elsewhere. The cytochrome P450 system isoenzyme 2D6 metabolizes tricyclic antidepressants, fluoxetine and paroxetine, beta-blockers, and several antiarrhythmic agents including encainide, mexiletine, and flecanide. This isoenzyme is inhibited by fluoxetine and paroxetine and, to a lesser extent, by sertraline. The P450 isoenzyme 3A4 is involved in the metabolism of lidocaine, quinidine, and calcium channel blockers including diltiazem, felodipine, nifedipine, and verapamil. It is inhibited by fluoxetine, fluvoxamine, nefazodone, and sertraline. Whether these interactions are clinically important is unknown. In addition, the 3A4 isoenzyme system metabolizes the non-sedating antihistamines terfenadine and astemizole. Inhibition of the metabolism of these compounds is associated with an increased risk of the potentially lethal ventricular tachyarrhythmia torsade de points.

In addition, effects on bleeding should be kept in mind, especially with the use of serotonin reuptake inhibitors and concurrent anticoagulation therapy. In one series of elderly cardiac rehabilitation patients, paroxetine and fluoxetine were associated with an increase in the INR in patients already taking warfarin. Berk and colleagues cite several case reports of
abnormal bleeding disorders in patients treated with fluoxetine or concurrent paroxetine and warfarin.

SUMMARY

Studies of community samples, psychiatric patients, and heart patients all support the hypothesis that depression is associated with ischemic heart disease. The association holds even after controlling for the confounding effect of smoking. Depression occurs commonly in heart disease patients and is strongly associated with heightened mortality after myocardial infarction. Thinking about the pharmacologic treatment of depression in ischemic heart disease patients has undergone dramatic change since the late 1980s, with increased appreciation of the probable mortality risk associated with tricyclic antidepressants because of their type 1A antiarrhythmic properties. The limited studies so far suggest that serotonergic antidepressants are well tolerated even in elderly ischemic heart disease patients, but their efficacy and safety remain to be further established. Their effects on platelet function are of special interest. Their use has also been suggested to reduce anger and its cardiovascular complications in ischemic heart disease patients, but the evidence of their value for this purpose is scant. Whether serotonergic antidepressants can reduce mortality in post-myocardial infarction depression is as yet unknown.

REFERENCES


