Depression in Patients Recovering From a Myocardial Infarction

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CASE PRESENTATION
A 56-year-old man was admitted to the hospital with an acute non–Q-wave myocardial infarction (MI). His course was complicated by postinfarction angina and 3-vessel coronary artery disease was found at angiography. He underwent uncomplicated coronary bypass graft surgery and was discharged 5 days later.

The patient had a history of hypertension and hyperlipidemia. He had no other significant past medical or psychiatric history. For the last 35 years, he worked 14 to 18 hours a day as a steel cutter doing “bull work,” which he said was “a constant strain on you.” The patient’s wife says he is a stubborn man who is “bullheaded.” Fourteen months before admission, he was wading with his wife by the seashore, complained of chest pain, slumped over, and had to be dragged ashore. He was brought by ambulance to the hospital, and shortly after arrival he left the hospital against medical advice because, “I always gotta’ go. I can’t sit still.”

Three weeks after his recent hospitalization, the patient was seen for routine follow-up. He reported feeling well and denied chest discomfort or shortness of breath. His only complaint was feeling “very bored.” Although he had a great deal of social contact with family and friends, he was spending most of the day in his house. He complained of being restless and bored because he thought he could not do his usual activities. He said that for many years he would experience low mood around holidays or anniversaries of deaths of family members but that this feeling was now present most of the day almost every day since hospital discharge. The patient said that he frequently cried now, often for no obvious reason. He reported feeling very unhappy and becoming disgusted with himself when he reflected on some aspects of his life that now appeared to him as a series of failures. He also experienced guilt about some of the possible effects his lifestyle had had on his health. He specifically said that his heart attack was his “fault because I didn’t take care of myself.” The patient did not report any change in appetite, weight, or sleep habits. He denied thoughts of harming himself or feeling that he would be better off dead.

After these symptoms were elicited, their importance was discussed with the patient and his wife. They were told that low mood is common after an MI and may adversely affect a person’s quality of life, overall sense of well-being, and ability to actively participate in recovery. It was noted that the importance of symptoms of depression after an MI is dependent primarily on their severity and efficacy are determined for antidepressant therapy in patients who recently have had an MI.

Depression soon after the event. Post-MI depression is an independent risk factor for increased mortality. Although the mechanism responsible for this association has not yet been defined, depression is clearly associated with poor compliance with risk-reducing recommendations, with abnormalities in autonomic tone that may make patients more susceptible to ventricular arrhythmias, and with increased platelet activation. Coronary revascularization procedures also appear to be used less often in those with post-MI depression than in comparable patients without mood disorder. Ongoing research will address whether treating depression improves prognosis. Until this question is answered, efforts should focus on enhancing adherence to treatment regimens in this group of patients, who are clearly at risk for noncompliance. Cardiac rehabilitation programs and increasing levels of social support may help improve symptoms and should be recommended to all patients. Treatment of depression itself should be individualized until safety and efficacy are determined for antidepressant therapy in patients who recently have had an MI.

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and duration. The patient and his wife were told that if his depressed mood began to affect his eating and sleeping habits or to impair his ability to concentrate, then specific treatment and referral to a mental health provider would be recommended. He and his wife were told that if he began to have thoughts of harming himself or wished he were dead, referral and treatment should be immediate and hospitalization may be indicated. They were told that they would be called to reassess the status of his mood disturbance in 1 week. The patient was informed that it was possible that his symptoms would improve over the next few weeks but that antidepressant therapy might be indicated if they did not.

Participation in a cardiac rehabilitation program was strongly recommended as being potentially helpful to his physical and emotional health. The patient enrolled in a phase 2 cardiac rehabilitation program, and his symptoms of depression were monitored by telephone calls and by the supervisor of the rehabilitation program. Both the patient and his wife noted improvement in his symptoms over the next few weeks.

**DISCUSSION**

Depression is manifested by a number of symptoms including (1) depressed mood, (2) diminished interest or pleasure in all, or almost all, activities, (3) low self-esteem, (4) sleep disturbance, (5) changes in appetite, (6) loss of energy, (7) difficulty concentrating, (8) psychomotor retardation or agitation, and (9) suicidal ideation. Major depression is diagnosed when 5 or more of these symptoms have been present most of the day nearly every day for more than 2 weeks. To diagnose major depression, at least 1 of the symptoms has to be either depressed mood, diminished interest, or diminished pleasure.1 Dysthymia is characterized by 2 or more of these symptoms present for more days than not for at least 2 years.

The Beck Depression Inventory (BDI) may be used to determine the presence and severity of symptoms of depression but is not appropriate for making the diagnosis of the syndrome of major depression. The BDI is a 21-item self-report questionnaire scored from 0 to 3 on each item. The total score ranges from 0 to 63, with higher scores indicating greater levels of distress. Although a patient who scores 10 to 20 points on the BDI would be considered to have symptoms of at least mild to moderate depression, such an individual would probably not meet criteria for a diagnosis of the syndrome of major depression. Nevertheless, even without a diagnosis of major depression, a patient with a BDI score of 10 or greater is at increased risk of post-MI mortality during the first 18 months after hospital discharge.3 Other easy-to-use rating scales are also available to assess depression, including the Hospital Anxiety and Depression Scale,4 which may be particularly useful for patients with physical illness, including MI.3 During the office visit 3 weeks after discharge from the hospital, the patient presented herein scored 14 on the BDI.

He had several symptoms of depression, including depressed mood and low self-esteem. Although there had been times in the past when he experienced these symptoms for brief periods, they had been persistent since his MI. The patient’s wife noted that he even cried the previous evening while they were watching The Highlander, a movie “about a man getting his head cut off.” The patient’s wife said he was sitting quietly and suddenly started crying at the theme song. Indeed, the patient cried during the office visit when he explained that the song “Who Wants to Live Forever?” is played as the main character, who is immortal, grieves over the death of the woman he loves.

Post-MI depression is common.5 Major depression is found in about 1 in 6 patients soon after MI and at least twice as many have significant symptoms of depression (TABLE 1).5,7-12 Most patients with major depression soon after MI will remain depressed months afterwards. More than 3 out of 4 individuals who are found to have major depression in the hospital soon after MI are still depressed 3 months later.7 By contrast, only about 1 of every 3 patients with less severe symptoms soon after MI, like the patient presented, are still depressed 3 months later.7 This does not diminish the potential importance of depressive symptoms after MI because even minor de-

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<td>268</td>
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<td>Ziegelstein et al,9 2000</td>
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<td>105</td>
<td>54</td>
<td>Men</td>
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*Ellipses indicate not applicable.
†Average age in study.
‡Total with major and minor depression.
§Major depression and/or dysthymia.
pressive symptoms may persist in some individuals, and it is unclear whether resolution of symptoms alters the association of even minor depressive symptoms with increased mortality.

The patient presented also had frequent contact with close family and friends, a factor that should be considered when deciding how to approach a patient recovering from an MI. Post-MI depression resolves more rapidly when patients have good social support. A recent study showed that, among those patients with depression (BDI >10) soon after MI who had high baseline social support, symptoms of depression improved to a greater than expected extent when reassessed 1 year later. Depressed patients who were unmarried, who lived alone, or who reported no close relatives or little contact with close friends and relatives experienced more symptoms of depression 1 year after the MI than would have been expected based on their baseline BDI score.

Thus, the patient presented herein, who is married, lives with someone, and reports frequent contact with close friends and relatives would be expected to have a more rapid improvement in his symptoms of depression than if he were socially isolated. It is important to note, however, that although high levels of social support predict a more rapid improvement, patients with post-MI depression with good social support may still require treatment for depression. The patient presented experienced fairly rapid improvement in his symptoms without antidepressant therapy. One month later, he reported few symptoms of depression and had a BDI score of 3.

Although post-MI depression is important to recognize because of its effect on quality of life, its presence takes on greater significance given its reported association with increased morbidity and mortality. Several groups have now documented an association between depression soon after an MI and mortality at 4 months, 6 months, 12 months, and 18 months. In a study of 222 patients interviewed approximately 1 week after an MI, Frasure-Smith et al found a significant increase in 6-month mortality rates among patients who were depressed soon after MI, even after controlling for left ventricular dysfunction and previous MI. Indeed, the mortality risk of post-MI depression reported in this study was as great as that associated with other recognized prognostic indicators, including left ventricular dysfunction, diabetes mellitus, age, and ventricular tachycardia. Welin et al found that the association of depression soon after an MI and increased mortality was still present 10 years later. Both Welin et al and Frasure-Smith et al found that the association of baseline depression and post-MI mortality was present even after adjusting for the effects of other established predictors of mortality in a multivariate analysis.

On the other hand, some authors have found that the association of depression and post-MI mortality loses significance when adjusting for other predictors of mortality or for potentially confounding symptoms, like fatigue, that may be common to depression and heart disease. Two other groups failed to find an association between depression and mortality at 4 months, 6 months, 12 months, or 18 months. Some have therefore concluded that it is premature to place depression alongside other independent risk factors for mortality after an MI without additional studies that rigorously control for disease severity and accurately identify and measure potential confounders of this relationship.

Increased Mortality

post-MI Depression and Increased Mortality

Depression is a risk factor for noncompliance in many medical conditions. A recent meta-analysis indicates that patients with depression are 3 times as likely to be noncompliant with medical treatment regimens than patients without depression. Several psychological factors, including depression, have been associated with poor compliance with advice to adopt an exercise program in patients recovering from an acute coronary event. Other studies have shown that patients with depression have a greater dropout rate from cardiac rehabilitation programs and demonstrate poor adherence to prescribed aspirin therapy for secondary prevention in the treatment of coronary artery disease.

When interviewed 4 months after discharge from a hospitalization for an acute MI, patients with baseline depression reported that they followed recommendations to reduce cardiac risk less often than patients who were not depressed. Compared with those with a BDI score of less than 10, patients with a BDI score of 10 or higher soon after MI indicated 4 months later that they were less often following a low-fat diet, exercising regularly, or making attempts to reduce their levels of stress or increase their social support. Those
with major depression and/or dysthymia during the initial hospitalization reported lower adherence to these recommendations and also reported taking medications as prescribed less often than those without major depression and/or dysthymia. Patients with major depression and/or dysthymia who had diabetes mellitus indicated that they followed a diet for patients with diabetes less often than those without depression.

The potential effect of these findings on post-MI mortality should be viewed in the context of a recent review article that indicated that medication nonadherence has a negative effect on morbidity and mortality among patients with or at risk for coronary artery disease or congestive heart failure. In the Beta-Blocker Heart Attack Trial, which studied the effect of propranolol on mortality in survivors of acute MI, patients who did not adhere well to their prescribed treatment regimen (defined as those who took ≤75% of their prescribed medication) were almost 3 times as likely to die in the first year of follow-up than those who were considered good adherers. The finding that depression decreases the likelihood that patients will make attempts to increase their social support is important in light of recent findings that social support may buffer the effects of depression on prognosis. In a study of 887 patients who completed both the BDI and the Perceived Social Support Scale approximately 1 week after an MI, the relationship between depression (BDI score ≥10) and 1-year cardiac mortality decreased with increasing levels of social support. The 1-year cardiac mortality of depressed patients with the lowest levels of perceived social support was at least 5 times that of depressed patients with the highest levels of perceived social support. Indeed, among patients in the highest quartile of perceived social support, the association between depression and increased mortality was no longer present.

In addition to this effect of post-MI depression on behavior, there may be an effect of depression on biological factors that may make the patient more susceptible to cardiac arrhythmia or to myocardial ischemia. There appears to be an interplay between emotional state and ventricular irritability after an MI. Although the presence of frequent premature ventricular contractions (PVCs) after an MI is generally considered to be a predictor of increased mortality risk, the 18-month post-MI mortality rates of patients with frequent PVCs (≥10 per hour) on Holter monitoring and who were not depressed was similar to those without frequent PVCs. On the other hand, patients with a BDI score of 10 or more and frequent ventricular ectopy were found to have a mortality risk that was significantly greater than the rest of the population studied (odds ratio, 29.1; 95% confidence interval, 6.9-122.0; P < .001).

The effect of depression on autonomic tone may also contribute to the increased mortality risk in post-MI patients. Low heart rate variability (HRV) indicates abnormally high sympathetic tone with or without abnormally low parasympathetic neurological input to the heart. Low HRV has been established as an independent predictor of increased mortality in patients after an MI. In a recent study, depressed patients with coronary disease were found to have significantly lower HRV than age- and sex-matched patients with coronary disease who were not depressed. Interestingly, treatment of patients with coronary artery disease who also had moderate to severe depression (BDI score ≥20) with cognitive behavioral therapy lowered the average resting heart rate and increased the daytime root mean square successive difference of normal-to-normal intervals, an index of HRV.

Individuals with depression have also been found to have evidence of increased platelet activation. If these abnormalities are present in patients with post-MI depression, then depressed patients recovering from an MI may be more susceptible to recurrent myocardial ischemia than those patients without depression. In a recent study, platelet activation under basal conditions was increased in subjects with major depression compared with control subjects as demonstrated by increased platelet binding of the monoclonal antibodies antiligand-induced binding site and the monoclonal antibody GA6 and increased plasma concentrations of platelet factor 4. Antidepressant therapy using the selective serotonin reuptake inhibitor (SSRI) paroxetine was associated with normalization of these measures of platelet activation such that after 6 weeks of drug treatment, these values were no different from the baseline values of control subjects. Another recent study showed that platelet activation, as assessed by in vitro platelet secretion in response to collagen, was increased in depressed subjects compared with those from age- and sex-matched control subjects without depression. The increased platelet activation in depressed subjects was significantly reduced after 6 weeks of treatment with the SSRI sertraline. These findings may reflect an abnormality of agonist-receptor coupling in circulating platelets of patients with depression. Platelets from depressed subjects demonstrate a greater increase in intracellular calcium following agonist stimulation than do platelets from those without depression.

This enhanced response in intracellular signaling was attenuated in the platelets isolated from depressed patients receiving an SSRI. The differences in intracellular calcium levels may be secondary to changes in agonist-receptor interactions on the platelet cell membrane. As is the case in many types of cells, receptor stimulation in platelets is followed by hydrolysis of membrane phospholipids and by increases in levels of inositol phosphates that then mediate the actions of the stimulus inside the cell. One of the major pathways stimulated in this manner involves the second messenger inositol 1,4,5-trisphosphate, which increases intracellular calcium levels by releasing calcium from intracellular stores. Of note, levels of inositol phosphates in the platelets of drug-free patients with depression were found to be higher after receptor stimulation by either epinephrine or thrombin than they were in the...
platelets of age- and sex-matched control subjects without depression. On the other hand, when platelet inositol phosphate levels were increased by stimulation with sodium fluoride, which does not bind to a receptor, no differences between platelets from depressed patients and those from control subjects were found. This suggests that there is a defect in receptor-agonist coupling in the platelets of individuals with depression that may make these platelets more likely to be activated.

In addition to the abnormalities that may be found in patients with depression that place them at greater risk, it also appears that patients with post-MI depression do not undergo potentially beneficial treatments as often as individuals without depression. A recent study examined the association between the presence of mental disorders and the use of cardiac catheterization and coronary revascularization procedures in a national cohort of 113,653 patients 65 years or older with an acute MI. This study found that patients with mental disorders were less likely to undergo percutaneous coronary intervention or coronary artery bypass graft (CABG) surgery than those without mental disorders. Among patients with major affective disorder, which includes those with major depression, the unadjusted use of percutaneous coronary intervention was 9.2% and that of CABG surgery was 7.9% compared with 16.8% and 12.6% in those with no mental disorder.

**Treatment Strategies for Depression in Patients Recovering From MI**

Whether treating depression can reduce the morbidity and mortality risk among patients recovering from an MI is unknown. To address this question, the National Heart, Lung, and Blood Institute has sponsored the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) study, which is a multicenter, randomized clinical trial investigating the effects of a psychosocial intervention on mortality and non-fatal MI in patients with an acute MI who are depressed or have low perceived social support. The safety and efficacy of antidepressant drug treatment in patients who have recently experienced an acute MI is still unknown. The multicenter Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) is examining this question. Although this study will provide important information on the effects of antidepressant drug therapy soon after an acute MI, the existing literature suggests that the SSRIs are safer in patients with heart disease than the tricyclic antidepressants (TCAs).

The TCAs have several cardiovascular effects that are undesirable in patients with heart disease, including their tendency to increase resting heart rate, produce orthostatic hypotension, and alter intracardiac conduction and the susceptibility to ventricular arrhythmias. The effects of TCAs on cardiac rhythm and conduction are similar to the type 1 antiarrhythmics quinidine and moricizine. There is therefore concern that the TCAs may increase mortality in patients with heart disease, as did moricizine in the Cardiac Arrhythmia Suppression Trial II (CAST II) and quinidine in other studies. It has therefore been suggested that the TCAs should be avoided in patients with ventricular arrhythmias or ischemic heart disease.

By contrast, the early experience in patients with SSRIs and ischemic heart disease, some of whom were treated soon after MI, suggests that these agents are safe and effective. In a study of patients with ischemic heart disease and major depression, the effects of 6 weeks of antidepressant therapy with the SSRI paroxetine were compared with the effects of the TCA nortriptyline for the same duration of treatment. Of note, patients were specifically excluded from this study if they had sustained an MI within the past 3 months. Paroxetine and nortriptyline were both associated with improvements in symptoms of depression. Although the SSRI did not affect resting heart rate or HRV, patients treated with the TCA had significant increases in heart rate and reductions in HRV. Those patients treated with nortriptyline also experienced significantly more adverse cardiac events than those treated with paroxetine. In a double-blind, placebo-controlled study, patients with major depression soon after MI were treated with the SSRI fluoxetine. Patients were randomized to receive fluoxetine or placebo for the first 9 weeks of the study and those who wished to continue participating and did not have serious adverse events were given fluoxetine or placebo for an additional 16 weeks. Fluoxetine resulted in improvement in symptoms of depression, particularly in those with mild depression at baseline, without producing changes in cardiac function as assessed by electrocardiography and echocardiography. In another study, sertraline was used to treat 26 patients with major depression soon after an MI. During treatment with sertraline, depression improved and no significant changes in heart rate, blood pressure, cardiac conduction, left ventricular ejection fraction, or ventricular ectopy were observed. Taken together, these studies indicate that compared with TCAs, the SSRIs are the preferred class of antidepressant medications in patients with post-MI depression.

Although antidepressant therapy is often required to treat post-MI depression sufficiently and prevent relapse, cardiac rehabilitation is also an important part of the care of patients after an MI, whether they are depressed or not. Many aspects of psychological health are improved by cardiac rehabilitation, including symptoms of depression. In a study of 338 patients, 75 of whom had recently experienced an MI, the prevalence of depressive symptoms was significantly reduced after a 12-week phase 2 cardiac rehabilitation program among the 69 patients (20%) who were depressed at the time of referral shortly after a major cardiac event. In this study, depression was defined as a score of greater than 6 on the Symptom Questionnaire. On this questionnaire, a score of 7 to 9 is considered to repre-
sent moderate depressive symptoms and a score of 10 or greater is considered severe. Among the depressed patients, the score on the Symptom Questionnaire improved from an average of 11.2 at baseline to 5.1 after rehabilitation ($P = .001$). Although there was no control group in this study to permit the effects of the rehabilitation program to be specifically determined, the rehabilitation program had other positive effects in the group with depression that were at least as significant as the effects noted in patients without depression. Before entry into the rehabilitation program, depressed patients had significantly lower exercise capacity than those patients without depression (4.9 vs 5.8 metabolic equivalents [METs], $P = .01$). Although individuals without depression experienced a 36% increase in exercise capacity after the 12-week program (from 5.8 to 7.9 METs), individuals with depression experienced a 51% increase (from 4.9 to 7.4 METs, $P = .001$ for each).

In another study, 268 consecutive patients older than 65 years with heart disease were prospectively studied after enrollment in a cardiac rehabilitation program. Of these, 64 were post-MI and 48 (18%) were depressed. Among the depressed patients, the score on the Symptom Questionnaire improved from an average of 10.4 at baseline to 4.5 after rehabilitation ($P = .001$).

**CASE RESOLUTION**

The patient presented herein was strongly encouraged to enter a phase 2 cardiac rehabilitation program and participated for several weeks before he returned to work. The patient’s physical and emotional health were closely assessed and followed up in the cardiac rehabilitation program, and his progress was also monitored on a weekly basis by telephone contact. Since his symptoms rapidly improved, antidepressant therapy was not recommended. Such close monitoring and observation are not always possible, particularly since many patients do not enter cardiac rehabilitation programs and depressed patients have a particularly high dropout rate. Even with these measures, many patients do not improve without antidepressant therapy. It also must be remembered that even mild symptoms of depression are associated with increased post-MI morbidity and mortality. This patient’s rapid improvement persisted, and he is still doing well now 10 months later.

**The Importance of Enhancing Compliance**

There are 2 critical, but as yet unanswered, questions raised by this discussion: (1) what is the mechanism linking depression and increased post-MI mortality, and (2) will treating depression affect this association? Unfortunately, the answers to these questions will not likely be known for at least several years. While we are awaiting the results of the clinical trials that address these questions, it is important to use what we know to optimally manage high-risk patients with post-MI depression. It is very clear from the evidence that depression should be considered a risk factor for noncompliance in patients with heart disease. The American Heart Association has emphasized the importance of improving compliance to achieve better clinical outcomes. In her address to the association’s 70th Scientific Session, past president Martha Hill, PhD, RN, spoke of the gaps between the potential benefits to health suggested by the results of clinical trials and the actual benefits achieved in practice. Hill emphasized that these gaps could be narrowed by a marriage between the social and behavioral sciences and the biological sciences. The studies indicating that depression adversely affects the compliance with therapy of patients with coronary heart disease suggest that compliance-enhancing initiatives targeted to this group may, if successful, favorably affect the relationship between post-MI depression and poor outcomes.

Several years from now, many of the questions about post-MI depression will be answered. The safety and efficacy of antidepressant drug therapy in patients early after an MI will be known. The benefits of strategies treating depression itself or of strategies targeting the effects of depression on platelet activation or ventricular arrhythmia will be clearly defined. However, if the compliance problems remain unaddressed, the benefits of this research may not reach the very population they are intended for and the relationship of post-MI depression to increased mortality will not have been affected.

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