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# Depression and Coronary Heart Disease: A Review for Cardiologists

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**Summary:** Major depression is a common comorbid condition in patients with coronary heart disease (CHD). Although mild emotional distress may be a normal reaction to myocardial infarction or other manifestations of CHD, major depression should not be considered a normal reaction, nor should it be ignored. Major depression is a debilitating comorbid disorder that can seriously complicate recovery and increase the risks of further cardiac morbidity and mortality. Fortunately, it is one that can be successfully treated in the majority of cases. The purpose of this review is to present the evidence for the negative prognostic effects of depression in cardiac patients and to discuss methods for assessing and treating depression in these patients.

**Key words:** depression, coronary heart disease, emotional distress, treatment

## Introduction

Psychiatric depression is both a common precursor and a common sequela of major cardiac events. Up to 65% of patients report depressive symptoms following acute myocardial infarction.[1–3] In many cases, these are merely symptoms of a normal adjustment reaction or mild depressive episode that may resolve within a few days or weeks of the myocardial infarction. In other cases, however, these symptoms constitute the prodromal phase of a more serious and persistent depressive disorder.

Major depression, a relatively severe depressive disorder, affects approximately 16 to 22% of patients who have suffered a recent myocardial infarction.[4–7] Major depression is also common in patients who have never had a myocardial infarction or any other significant cardiac event, but who do have angiographically proven coronary artery disease. The prevalence is estimated to be about 18% in these patients.[8] By contrast, the 1-month prevalence of major depression in the community is estimated to be approximately 4.9%.[9]

Depressive disorders are important not only because they are common in patients with coronary heart disease (CHD), but also because there is compelling evidence that they portend increased medical and psychosocial morbidity and mortality, even after adjusting for the severity of the coronary disease or the size of the myocardial infarction. The purpose of this review is to present evidence for the negative prognostic effects of major depression in cardiac patients and to discuss methods for assessing and treating depression in these patients.

## What Is Major Depression?

Major depression is a prevalent mental health problem with which most practicing physicians are very familiar. It is often surprisingly difficult to identify, however, because it presents in a variety of different forms and because there is not yet a definitive laboratory test for it. The differential diagnosis of depressive disorders depends upon assessment of the pattern, severity, and duration of symptoms. The most widely accepted symptom-based criteria for diagnosing depression and other psychiatric disorders are found in the Diagnostic and Statistical Manual of Mental Disorders.[10]

Along the spectrum of depressive disorders, *adjustment reaction with depressed mood* is the mildest and most transient. It follows in the wake of identifiable stressors (e.g., myocardial infarction) and persists no longer than 6 months after the stressor(s) have terminated. Its symptoms consist of relatively mild emotional distress and limited social, occupational, or other functional impairment. Patients with an adjustment reac-

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tion may require no more than encouragement and optimism from their physician and perhaps occasionally a referral for supportive counseling or psychotherapy.

In contrast, *a major depressive episode* may be present when five or more of the symptoms presented in Table I, one of which must be either depressed mood or loss of interest, persist for at least 2 weeks and cause clinically significant distress or functional impairment. The onset of a major depressive episode cannot always be linked to emotionally stressful events or to any other identifiable precipitating factors, but sometimes it can be.

## Natural History of Depression in Patients with Coronary Heart Disease

Major depression is a debilitating comorbid disorder that typically persists for months if left untreated and can seriously complicate recovery from myocardial infarction. In many cases, a major depressive episode was already in progress at the time of the myocardial infarction; in others, the myocardial infarction may have precipitated the depressive episode. Regardless of whether the onset of the depressive episode occurs before or after a myocardial infarction, it tends to follow a chronic course during the first year after discharge from the coronary care unit.[7, 11, 12] Major depression also tends to be quite persistent in patients who have not had a recent cardiac event but who do have stable coronary artery disease.[13]

Whether treated or untreated, many patients relapse while recovering from major depressive episodes. Relapses are particularly common among postinfarction patients whose depression does not fully remit.[14] Patients are not considered to have fully remitted until there have been no significant signs or symptoms of major depression for at least 2 months.[10]

TABLE I Abbreviated diagnostic criteria for major depressive disorder

Five or more of the the following symptoms of major depressive disorder have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms must be either depressed mood or loss of interest or pleasure.

1. Depressed mood
2. Markedly diminished interest or pleasure in almost all activities
3. Significant changes in appetite or weight
4. Insomnia (or, in some cases, hypersomnia)
5. Psychomotor agitation or retardation
6. Fatigue
7. Feelings of worthlessness or excessive guilt
8. Diminished ability to think, concentrate, or make decisions
9. Recurrent thoughts of death or suicide, which are often accompanied by a sense of hopelessness

The symptoms must cause significant distress or impairment in social or occupational areas of functioning and cannot be due to the effects of medications.

Please refer to manual in Ref. 10 for complete criteria.

Unfortunately, recurrences months or years after complete remission are not uncommon.

## Effects of Depression on Functioning and Prognosis

Major depression is as debilitating as heart disease. The Medical Outcomes Study[14, 15] showed that depression causes as much disruption to daily functioning as most common chronic medical conditions, including heart disease, hypertension, diabetes, and chronic lung disease. On measures of functional disability, depression resembles heart disease more than any other chronic medical condition because both of them affect every domain of health-related quality of life. Furthermore, depression and chronic medical conditions such as heart disease have additive adverse effects on functioning and well-being. The combination of advanced coronary artery disease and depressive symptoms was associated in the Medical Outcomes Study with roughly twice the social impairment caused by either condition alone. A more recent study of 25,916 attendees of primary healthcare facilities in 14 countries confirmed the poor level of functioning of depressed patients found in the Medical Outcomes Study, and extended these results across other cultures.[16]

The psychosocial effects of depression in patients with CHD are well documented. Depressed patients post myocardial infarction are more likely to experience social problems over the first year of recovery, are slower to return to work, and report more stress than their nondepressed counterparts.[2, 17, 18] Depression is also associated with poor social adjustment following coronary bypass surgery.[19] In patients with congestive heart failure, depression is a stronger predictor of New York Heart Association functional class than is left ventricular ejection fraction.[20]

There is also considerable evidence that major depression has adverse effects on medical prognosis in cardiac patients. This may also be true of less severe depressive syndromes. In a study of patients undergoing diagnostic cardiac catheterization and arteriography, for example, concomitant major depression was the best predictor of cardiac events over a 1-year follow-up.[21] Similarly, patients who are depressed following a recent myocardial infarction are at increased risk for subsequent cardiac events, including reinfarction and rehospitalization, compared with those without depression.[22] A study of 222 patients by Frasure-Smith *et al.* found that depression was associated with a more than four-fold increased risk of mortality during the first 6 months following acute myocardial infarction after adjusting for relevant covariates including left ventricular dysfunction.[23] Moreover, its prognostic significance was equivalent to that of left ventricular dysfunction and previous history of myocardial infarction.

Comorbid depression may be particularly risky for patients with certain cardiac arrhythmias. It has been associated with increased mortality rates in patients being evaluated for the treatment of ventricular arrhythmias.[24] In the Cardiac Arrhythmia Pilot Study (CAPS), a controlled trial of antiarrhythmic therapy in patients post myocardial infarction at high risk for

sudden cardiac death, depression was found to be a significant risk factor for resuscitated cardiac arrest or death, after adjusting statistically for clinical predictors of disease severity.[25] Finally, Ladwig *et al.* found that depression predicted an increased risk of sudden cardiac death and arrhythmic events in a sample of 560 male survivors of acute myocardial infarction during a 6-month follow-up.[26]

Although the mechanism(s) linking depression to increased risk for cardiac events are not fully understood, biological studies of depression have provided important clues. Increased sympathetic and decreased vagal tone have been found in depressed but otherwise medically well psychiatric patients.[27–29] Altered autonomic tone is known to increase the risks for myocardial infarction, sudden cardiac death, and other cardiac events in vulnerable individuals.[30,31]

There is increasing evidence that altered autonomic tone is also present in depressed cardiac patients. For example, we have shown that depressed patients with CHD have elevated mean heart rates and reduced heart rate variability compared with nondepressed patients with CHD, even after adjusting for relevant covariates.[21,32] Consistent with this putative mechanism, depressed patients with CHD have been found to have more frequent and longer runs of ventricular tachycardia compared with non-depressed patients with CHD.[33]

## Recognition of Depressive Disorders

The importance of treating major depression in cardiac patients is becoming increasingly obvious as more is learned about its negative prognostic implications. Nevertheless, it is seldom diagnosed in cardiac patients, and it is even more rarely treated. It has been repeatedly shown that physicians correctly diagnose less than one out of four cases of major depression in cardiac patients and that only about half of the diagnosed patients ever receive treatment.[8,34]

There is less evidence for the necessity of treating milder depressive syndromes in cardiac patients, but they are not always transient or innocuous. In fact, a case of mild depression that seems to be within normal limits for an acutely ill cardiac patient is almost as likely to be the prodrome of a major depressive episode as it is to remit without further complications.[13] Thus, cardiac patients with initially mild, depressive adjustment reactions or with too few symptoms to meet criteria for major depression should either be treated prophylactically or contacted at frequent intervals to determine whether they are developing major depression.[35] Initially, reevaluation of depressive symptoms may be necessary as often as once or twice per month. An interview with the spouse or other caregiver can also be very informative in determining whether the patient is becoming more severely depressed. Most important, if it is decided that the patient is indeed clinically depressed, optimism is warranted, as effective treatments are readily available.

Recognizing depression after a coronary event is often difficult for both patient and physician. One problem in making the diagnosis is that there is considerable overlap between the symptoms of depression and those of CHD.[36] Fatigue and insomnia, for example, are common symptoms not only of depression but also of cardiac disease. However, the most important barrier to proper diagnosis and treatment of depression in these patients may be the common misconception that depression in such a situation is an expected, normative reaction rather than a serious but treatable mental disorder.[35] Unfortunately, this mistaken belief is widely held by physicians and patients alike. Many patients may be reluctant to report depressive symptoms to their physician unless invited to do so, and many physicians may be reluctant to ask.

A variety of brief questionnaires and interview forms are available to assist physicians in screening for depression. For example, the Beck Depression Inventory[37] is a 21-item self-report questionnaire on which a score of 10 or higher is suggestive of at least mild depression. The Primary Care Evaluation of Mental Disorders[38] (PRIME-MD) is designed to enable physicians to screen rapidly not only for depression but for a variety of other mental disorders as well. Routine use of such instruments could markedly improve the chances that physicians will detect cases of depression that might otherwise be overlooked.

## Treatment of Depression in Patients with Coronary Heart Disease

When a diagnosis of major depression has been made, the risks and benefits of treatment must also be carefully considered in view of the patient's concomitant heart disease. Selected tricyclic antidepressants (TCAs) have been used successfully to treat major depression in many patients with heart disease.[39] However, these agents are known to affect cardiac conduction, contractility, rate, and rhythm.[39–42]

The most common cardiovascular side effect in patients with coronary heart disease is orthostatic hypotension.[42,43] This is a particular concern for elderly patients, especially those who are also receiving cardiac medications such as calcium-channel blockers, alpha-adrenoceptor antagonists, diuretics, or beta blockers. Tricyclic antidepressants may add to the antihypertensive effects of these drugs. The orthostatic hypotensive effect of TCAs is most pronounced in patients with conduction disorders, especially bundle-branch block, and in patients with congestive heart failure.[44] In addition, TCAs may further impair conduction in patients who have cardiac conduction abnormalities.[40]

Contrary to expectation, certain TCAs have been found to have antiarrhythmic effects.[40,43,45] However, the combination of TCAs with antiarrhythmic medications has not been adequately studied. Thus, there is concern that the quinidine-like effects of the TCAs might interact with other antiarrhythmic medications in potentially harmful ways.

Selective serotonin reuptake inhibitors (SSRIs) are as effective as the tricyclics in treating depression and have been a recent focus of attention mainly because of their improved safety profiles. A randomized trial of 81 patients with ischemic heart disease found the selective serotonin reuptake

inhibitor paroxetine to be as effective but better tolerated than the tricyclic antidepressant nortriptyline in the treatment of depression.[46] As SSRIs have little affinity for cholinergic, histaminergic, or adrenergic receptors, they cause fewer anticholinergic, sedative, hypotensive, and other adverse cardiovascular reactions than do TCAs.[47]

Although relatively safe in patients with cardiac disease, SSRIs are known to interact with other medications by inhibiting the activity of specific P450 liver enzymes which are involved in their metabolism. Potential drug interactions include medications commonly prescribed for cardiac patients, such as beta blockers, warfarin, and type 1C antiarrhythmics.[48] Different serotonin reuptake inhibitors interact with different medications, so potential interactions can generally be avoided by carefully selecting the SSRI. However, whenever an SSRI is administered with any other agent that is metabolized by the same cytochrome P450 enzymes, it is important to start with a conservative dosing schedule and then to monitor the patient carefully.

Because SSRIs are comparatively safe, they are the treatment of choice for most cases of major depression in patients with cardiac disease, except for patients who have been successfully treated in the past with a different agent. Among the TCAs, nortriptyline has the advantage of having a well-described plasma concentration therapeutic window (50–150 ng/ml), and its blood level can be monitored so that an adequate therapeutic level can be maintained. However, as discussed earlier, TCAs are contraindicated in some patients with a conduction disorder or orthostatic hypotension. Other agents which, unlike the tricyclics, do not have anticholinergic effects include bupropion, which is relatively activating, and trazodone and nefazodone, which are more sedating. However, trazodone has potent hypotensive effects. A list of commonly used antidepressants and the recommended starting doses for elderly patients are presented in Table II. The upper limits of the therapeutic dosages presented in this table are significantly higher than are needed in most cases. Furthermore, many elderly patients cannot tolerate such high doses of these agents.

Although there have been no studies of the effects of treating depression on psychosocial or medical outcomes in patients with heart disease, there is evidence that treatment generally does improve psychosocial functioning. Studies in primary care settings have shown that whereas disability persists in untreated patients with chronic depression or anxiety, it decreases when these mood disorders are successfully treated.[49,50]

TABLE II Common antidepressant medications

| | Generic name | Brand name | Starting dose | Therapeutic dose |
|---|---|---|---|---|
| SSRIs (mg/day) | Sertraline | Zoloft | 25–50 | 50–200 |
| | Paroxetine | Paxil | 10–20 | 10–40 |
| | Fluoxetine | Prozac | 10–20 | 10–40 |
| | Fluvoxamine | Luvox | 25–50 | 50–200 |
| TCAs (mg/day) | Nortriptyline | Pamelor | 10–25 | 50–150 |
| | Imipramine | Tofranil | 25–50 | 100–300 |
| Other (mg/day) | Bupropion | Wellbutrin | 75 | 150–400 |
| | Trazodone | Desyrel | 25–50 | 150–300 |
| | Nefazodone | Serzone | 25–50 | 200–600 |
| | Venlafaxine | Effexor | 75 | 75–225 |

*Abbreviations:* SSRIs = serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.

## Conclusions

Although mild emotional distress may be a normal reaction to myocardial infarction and other manifestations of coronary heart disease, clinical depression definitely is not. Major depression is a debilitating comorbid disorder that can seriously complicate recovery and increase the risks of further cardiac morbidity and mortality. Fortunately, it is a disorder that can be successfully treated in the majority of cases. The prognostic implications of an adjustment reaction with depressed mood are less clear, as is the need for treatment. However, depressive symptoms can affect functioning and can often herald a more serious major depressive episode. Thus, patients with adjustment reactions should be carefully monitored. For those patients who develop a major depressive episode, treatment usually is necessary and warranted. With proper precautions, selective serotonin reuptake inhibitors offer a relatively safe, effective form of treatment for major depression in patients with coronary heart disease.

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