Consensus Statement on Depression, Anxiety, and Cardiovascular Disease

James C. Ballenger, M.D.; Jonathan R. T. Davidson, M.D.; Yves Lecrubier, M.D.; and David J. Nutt, M.D., Ph.D. (International Consensus Group on Depression and Anxiety); and Steven P. Roose, M.D.; and David S. Sheps, M.D.

Depressive disorders and cardiovascular conditions are closely interrelated. Compared with the general population, individuals suffering from depression have an increased risk of sudden cardiovascular death, and the risk is highest in the presence of concomitant cardiovascular disease.[1,2] Similarly, patients with cardiovascular disease suffer from major depression more frequently than expected. More than 20% of subjects with angiographic evidence of coronary heart disease have concomitant major depression. Also, up to 20% of survivors of recent acute myocardial infarction meet diagnostic criteria for major depression, and the presence of depression is associated with an increased 6-month mortality, compared with nondepressed survivors.[3–8]

At our consensus meeting on depressive and anxiety disorders in general medicine, the International Consensus Group on Depression and Anxiety reviewed depression, anxiety, and the cardiovascular system from the perspectives of both the cardiologist and the psychiatrist. This article sets forth our views on the management of comorbid depression and anxiety in the cardiovascular patient on the basis of the current state of knowledge and identifies areas of further research.

DEPRESSION AND ANXIETY AS RISK FACTORS FOR CARDIOVASCULAR DISEASE

Good evidence indicates that clinical depression is an independent risk factor for the development of coronary artery disease,[9,10] and equally compelling evidence indicates an association between anxiety and coronary artery disease.[11] It is not yet known whether patients with more severe depression develop more severe cardiovascular disease, but there are data showing that patients with more severe anxiety develop more severe cardiovascular disease. In a large study of male health care professionals, Kawachi et al.[12] showed an association between panic phobic symptoms and an excess risk of sudden cardiovascular death.

Anxiety disorders, such as panic disorder and phobic disorder, often start early in life and develop chronically. They frequently lead to secondary depression and are a risk factor for the development of cardiovascular disease and for later sudden cardiac death. The presence of an anxiety disorder can bring people into a high-risk group at an earlier age in their life.

Depression is not only a risk factor for cardiovascular disease but is also a strong predictor of mortality in patients with manifest ischemic heart disease.[9] Among survivors of acute myocardial infarction, the increased risk of cardiovascular mortality is not restricted to patients with major depression but also extends to those patients with subsyndromal depressive symptoms. At 18 months after myocardial infarction, the mortality rate is reported to be the same in depressed patients who failed to meet full criteria for major depression as in those meeting criteria for major depression (17%).[13]

Vulnerability to cardiovascular risk increases with age in depressed patients, and it is most significant in the population aged over 60 years, which is the most rapidly growing segment of the world population. For example, a significant and substantial excess risk of death, myocardial infarction, or stroke in hypertensive patients aged over 70 years has been associated with an increase in depressive symptoms over time.[14] Also, elderly men (aged over 70 years) newly diagnosed with depression are reported to be almost twice as likely to have a cardiovascular event as men without a history of depression.[15]

It is accepted clinical practice that primary care physicians will consider risk factors for coronary artery disease when evaluating patients aged over 40 years and will intervene to decrease cardiovascular risk if they find hypertension, elevated cholesterol, or obesity. We feel strongly that depression and anxiety should be included in this model.

The International Consensus Group on Depression and Anxiety held the meeting "Focus on Depression and Anxiety Disorders in General Medicine," October 7–8, 1999, in Funchal, Madeira. The Consensus Meeting was supported by an unrestricted educational grant from SmithKline Beecham Pharmaceuticals.

Reprint requests to: James C. Ballenger, M.D., Medical University of South Carolina, Department of Psychiatry and Behavioral Sciences, 171 Ashley Ave., Charleston, SC 29425-0742.

As major risk factors for coronary artery disease, they should not be considered separately, but rather form part of the overall evaluation of cardiovascular risk factors by primary care physicians. Particular attention should be given to assessing mood disorders as contributors to cardiovascular risk in the population aged over 60 years.

We also want to emphasize the importance of improved monitoring of the cardiovascular status of depressed patients in primary care. Physicians should carefully monitor the cardiovascular status of any patient identified with depression.

Research Needs: Pathophysiologic models of the association between depression, anxiety, and cardiovascular disease implicate disturbed platelet function and reduced heart rate variability; further study is needed of these models in vulnerable populations. Further study of platelet activity is needed to establish what happens as younger depressed patients get older. A more extensive database of platelet activity over time is important, since the effects of depression may be long-term and not simply restricted to the index episode. Furthermore, in many patients depression becomes a chronic illness. It is known that a sustained increase in heart rate is associated with increased mortality in vulnerable populations such as patients with ischemic heart disease, but research is needed to define its effect in nonvulnerable populations. Research is needed on the relationship between traumatic stress and the subsequent development of psychiatric and medical disorders. For example, early trauma may permanently affect the hypothalamic-pituitary-adrenal axis and platelet vulnerability.

SCREENING FOR DEPRESSION AND ANXIETY

We recommend screening for depression and anxiety as part of the evaluation of risk factors for cardiovascular disease. Primary care physicians should apply a screening instrument for cardiovascular disease risk factors in the same way that they monitor blood pressure to detect hypertension. In our view, they should screen not only for major depression but also for symptoms that do not meet full diagnostic criteria.

There are many possible screening instruments, including the Mini-International Neuropsychiatric Interview (MINI),[16] the Primary Care Evaluation of Mental Disorders,[17] the Hospital Anxiety and Depression Scale,[18] and the Beck Depression Inventory.[19] The MINI has the advantage of being a short structured interview developed for use in 2 versions, based on DSM-IV or ICD-10 criteria. It can be used to detect both major depression and anxiety disorders.

Given that depression and anxiety also adversely affect prognosis in coronary artery disease, cardiologists and primary care physicians should screen their cardiac patients to identify these disorders. It is known that around 25% of patients with angiographic evidence of coronary artery disease will meet full diagnostic criteria for major depression, and major depression is the strongest single predictor of cardiac events in the 12 months after diagnostic coronary angiography.[3] In addition to patients with chronic stable coronary artery disease, other patients at high risk for depression include those with unstable coronary artery disease, unstable angina, and/or a history of acute myocardial infarction.

Given the relationship between age and susceptibility to cardiovascular risk, particular attention should be paid to older cardiac patients. It should also be remembered that depression and anxiety cause as much functional disability as physical illness,[20] so even in asymptomatic patients with coronary artery disease, the presence of comorbid depression and anxiety should be considered. Ameliorating depression and anxiety has been shown to improve patients' compliance with medication and adherence to lifestyle advice on diet and exercise from their physicians, and this in turn can have an impact on survival.[21]

There is a clear consensus that depression and anxiety are currently underdiagnosed in cardiac patients by cardiologists and primary care physicians alike. A possible reason for the low rate of detection is uncertainty among physicians about how to manage these disorders in cardiac patients if the disorders were identified. There are safe forms of treatment intervention (see section on management strategy). It remains speculative whether appropriate intervention in cardiac patients can improve not only psychiatric morbidity but also cardiovascular disease and decrease mortality, but we feel that there is a low risk and a potentially high gain from intervention with a safe treatment option.

Research Needs: Further research is needed regarding the most appropriate screening tool or tailored questionnaire for depression and anxiety in cardiac patients in a primary care setting.

MANAGEMENT STRATEGY FOR COMORBID DEPRESSION AND ANXIETY IN THE PATIENT WITH CARDIOVASCULAR DISEASE

The management strategy chosen must first consider the effect of treatment intervention on the underlying cardiovascular condition. The use of any medication that increases heart rate should be avoided in patients with manifest ischemic heart disease, as there are good data to show that increases in heart rate are more closely associated with mortality in these patients.[22] We take the view that it would also be judicious to avoid the use of such medication in vulnerable groups at high risk of developing heart disease, such as those with diabetes, obesity, hypertension, or elevated cholesterol.

Of the available antidepressant therapies, tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), the current treatments of choice for depression, have been studied in patients with cardiovascular disease. Tricyclic antidepressants have a range of cardiovascular effects. Orthostatic hypotension is a particular concern in the elderly, and slowing of cardiac conduction contraindicates the use of TCAs in patients with preexisting conduction problems. The Cardiac Arrhythmia Suppression Trial investigators[23,24] demonstrated that Type IA antiarrhythmic agents, such as TCAs, increase mortality in patients with ischemic heart disease. More recently, a trial comparing the TCA nortriptyline with the SSRI paroxetine[25] provides clear evidence that a therapeutic plasma level of TCA causes a sustained increase in heart rate, which makes TCA use problematic in the patient with compromised cardiovascular function. TCAs generally do not cause the same degree of cardiac complications in younger as in older patients, but in younger patients with increased parasympathetic activity, the effect of TCAs on heart rate variability is even greater than that found in older patients.

SSRIs have a benign cardiovascular profile by comparison with TCAs, as demonstrated by the study referred to above of paroxetine and nortriptyline in depressed patients with significant but stable ischemic heart disease.[25] SSRIs such as paroxetine are a relatively safe treatment option for depressed or anxious patients with cardiovascular disease. The increasing evidence for the efficacy of SSRIs in anxiety disorders, as well as depression, provides a further reason for physicians to consider a move toward their use in the cardiac patient with concomitant depression and anxiety.

Preferred Pharmacotherapy

SSRIs are the preferred treatment for depression and anxiety comorbid with cardiovascular disease, based on clinical data and cardiovascular profile. As comorbid depression and anxiety tend to be chronic, the treatment need is likely to be prolonged, and further data are needed on the long-term cardiovascular status of patients treated with SSRIs.

It is not yet known whether effective treatment of comorbid depression will also reverse disability and reduce the morbidity and mortality associated with manifest ischemic disease. There are certainly well-controlled trial data, notably on paroxetine, to support the safety of intervention with SSRIs. If a primary care physician or cardiologist detects major depression in a patient with cardiovascular disease, treatment with an SSRI, such as paroxetine, will likely relieve depressive symptoms and any concomitant anxiety with no evidence of risk and with the potential for improvement in the patient's cardiovascular profile. There is no reason *not* to treat the depressed cardiovascular patient with a safe drug that is likely to offer substantial benefits, certainly on psychiatric symptoms and secondary disability, and potentially on cardiovascular risk.

Psychotherapy

Cognitive-behavioral therapies are among the interventions that may be included in cardiac rehabilitation programs after myocardial infarction.[26,27] As yet, there is no conclusive evidence on the benefit of intervention with cognitive-behavioral therapy. However, the National Institutes of Health has sponsored a study (Enhanced Recovery in Coronary Heart Disease [ENRICHD]) of cognitive-behavioral therapy that should provide information on the effectiveness of this approach and help to define the place of psychotherapy in the overall management strategy for depression and anxiety in cardiac patients. The study has a 4- to 5-year follow-up, with provision for patients to receive drug treatment if initial treatment with cognitive-behavioral treatment is ineffective or patients experience relapse.

Research Needs: Two studies (the Sertraline Antidepressant Heart Attack Recovery Trial and ENRICHD) are currently ongoing and within several years will provide information on whether treating depression after myocardial infarction reduces mortality in patients with manifest ischemic disease. Research is also needed on whether early treatment intervention in the depressed cardiac patient can normalize platelet function and prevent the acceleration of cardiovascular risk. To gain further insight into the relationship between anxiety and cardiovascular risk, it is important to study a high-risk population that suffers from both anxiety and depression. Angioplasty patients have high degrees of both symptomatic anxiety and affective disorder and experience high recurrence of cardiac events over the first 1 to 2 years after the procedure. Comparing pathophysiologic measures, such as ischemia, heart rate variability, and platelet function, in patients treated with an SSRI or psychotherapy would be of great interest. This would help determine whether a reduction in cardiac mortality in treated depressed cardiac patients is due to an antiplatelet effect of the SSRI, independent of the antidepressant effect. Research is needed on the impact of treatment intervention on cardiovascular prognosis, since some clinical evidence suggests that not only major depression but also minor depression and depressive symptoms are associated with an increased risk of mortality in cardiac patients.

CLINICAL GUIDELINES FOR PRIMARY CARE MANAGEMENT OF COMORBID DEPRESSION, ANXIETY, AND CARDIOVASCULAR DISEASE

1. Depression and anxiety are risk factors for cardiovascular morbidity and mortality and should be the focus of treatment intervention, in the same manner as other accepted risk factors such as hypertension, elevated cholesterol, and obesity.

2. Patients should be routinely screened for depression and anxiety in primary care, analogous to blood pressure monitoring for hypertension.
3. In patients with manifest ischemic heart disease, there are as yet no data to support the positive effect of antidepressant treatment on cardiovascular mortality. However, risk-benefit analysis suggests that there is no reason *not* to treat cardiac patients with a safe drug: they would benefit from relief of their depression and a potential improvement in their cardiovascular risk profile.
4. There are well-controlled data, notably on paroxetine, to support the safety of treatment intervention with SSRIs in the cardiovascular patient with concomitant depression and/or anxiety. There is a low risk and potentially high gain to be derived from treating major depression in the cardiovascular patient with an SSRI, such as paroxetine. Intervention is particularly important in the myocardial infarction survivor and the elderly depressed patient with cardiovascular disease.
5. SSRIs are the preferred medications for depression and anxiety comorbid with cardiovascular disease, based on efficacy and cardiovascular safety data.
6. Treatment of depression with cognitive-behavioral therapy is potentially of great clinical and heuristic interest and is currently under investigation.

Drug names: nortriptyline (Pamelor and others), paroxetine (Paxil).

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