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Cardiovascular Risk Factors and Psychiatric Illness

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Cardiovascular Update

Abstract

Psychiatric illness and cardiovascular disease occur together more frequently than expected then by chance alone. Several of the established risk factors for coronary artery disease account for this increased risk of comorbidity. Psychiatric illness appears to increase the risk for hypertension. Smoking rates are higher in patients with psychiatric illness than for populations without psychiatric illness. Elevated serum cholesterol levels often occur in panic and other anxiety disorders. In contrast, there is accumulating evidence that low cholesterol levels are linked to violent death, including suicide. Myocardial infarction represents a major life stressor that can precipitate an episode of major depression. Prolonged depression following myocardial infarction can become an independent risk factor for cardiac mortality. These associations increase the need for psychiatrists to be aware of the risk factors for coronary heart disease and to assist with the assessment and management of these risk factors in patients with mental illness. © 1998 Elsevier Science Inc. *MEDICAL UPDATE FOR PSYCHIATRISTS 3;6:196–201, 1998.*

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Introduction

Cardiovascular disease continues to represent the leading cause of death in the United States. Although death rates from myocardial infarction appear to be decreasing, deaths from diseases of the heart still comprise 32% of all deaths in the United States (1). Identifying and reducing cardiovascular risk factors continues to present a significant public health challenge.

Psychiatric disorders appear to have several important links to cardiac disease and risk factors for coronary heart disease. First, some psychiatric disorders appear to increase risk for the development of known risk factors for cardiac disease, particularly hypertension and tobacco use. Second, major depression contributes to risk for cardiac mortality following a myocardial infarction. Third, low serum cholesterol and treatment of hypercholesterolemia may be associated with increased risk for violent death and suicide. Psychiatrists need to understand these associations to provide more comprehensive, high quality care for their patients.

Links between Psychiatric Illness and Cardiovascular Risk Factors

Hypertension

There is increasing evidence that depression may be an independent risk factor for hypertension. Jonas et al. (2) prospectively studied 3000 men and women without hypertension for periods of up to 16 years. High symptoms of depression at baseline predicted the development of hypertension in the followup period. Depression symptoms were assessed using the General Well Being depression subscale (3). This study was carefully controlled and found an independent effect of depression on risk for hypertension. Potentially confounding variables that were controlled in this study included: age, sex, education, smoking status, body mass index, alcohol use, and history of diabetes, heart disease, stroke, and baseline blood pressure.

Other psychiatric illnesses in addition to depression appear to increase risk for hypertension. Anxiety disorders appear to be associated with hypertension (4,5). Heavy drinking of alcohol has long been noted to increase blood pressure and reduce the effectiveness of antidepressant medication (6). Bipolar affective disorder has been linked to hypertension in one controlled study (7).

Cigarette Smoking

Cigarette smoking and nicotine dependence occur more frequently in a variety of psychiatric disorders. Breslau (8) reported the association of nicotine dependence with several psychiatric disorders in an epidemiologic study of 1000 young adults from southeast Michigan. Approximately 20% of this sample met lifetime criteria for nicotine dependence. Those with a diagnosis of nicotine dependence had increased risk for other substance dependence diagnoses including alcohol dependence and drug dependence. Nicotine dependence was also associated with major depression and anxiety disorders. Childhood conduct disorder symptoms predicted adolescent nicotine dependence. Breslau proposed that nicotine dependence is associated with the personality trait of neuroticism, a known risk factor for the development of depression.

The association of nicotine dependence with psychiatric disorders has also been found in an adoption study (9). In this study, 195 adoptees were interviewed for the presence psychiatric disorders, including nicotine dependence. Figure 1 demonstrates the odds ratios for various psychiatric disorders in those with a diagnosis of nicotine dependence. Mood disorders, anxiety disorders, and alcohol abuse or depen-

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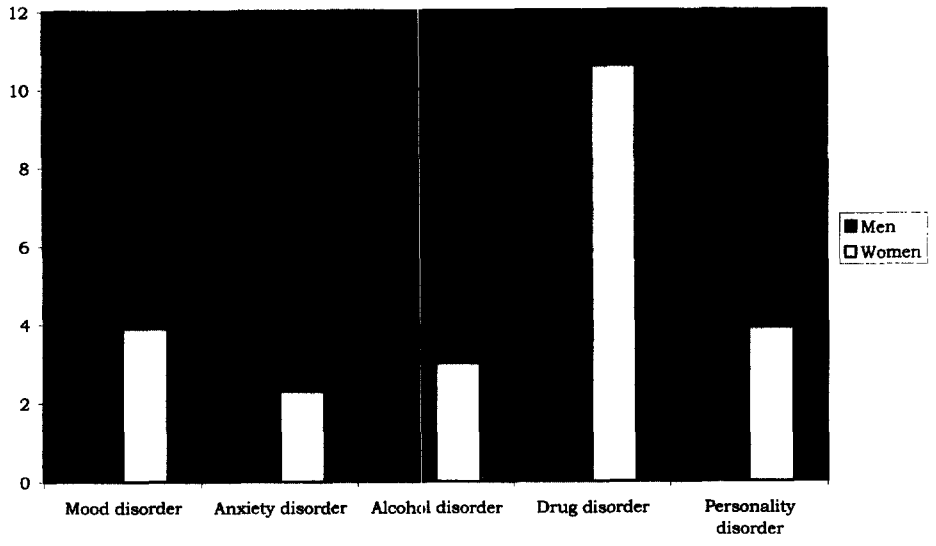

Figure 1. Odds ratios for psychiatric disorders in DSM-III-R nicotine dependence.

dence have odds ratios (ORs) of between 2:7 and 3:9. Higher ORs are noted for personality disorder (6:5) and drug abuse/dependence (8:2). Interestingly, non-dependent smokers did not appear to be at increased risk for many psychiatric disorders. This suggests that the development of heavy, dependent smoking is linked to risk for psychiatric illness rather than just smoking alone.

There are several clinical implications for the association of nicotine dependence to psychiatric illness. First, this association would predict high rates of psychiatric illness in patients with coronary artery disease related to smoking. Another implication is that psychiatric illness influences the natural history of smoking. Comorbid depression appears to reduce the likelihood of success with smoking cessation interventions. Nicotine dependent individuals with comorbid depression quit smoking at approximately 50% the rate for individuals without depression (10). However, a newer antidepressant medication, buproprion, appears to increase smoking cessation rates for individuals with or without comorbid depression (11).

Serum cholesterol levels may also be linked to some psychiatric disorders. Two studies demonstrated higher serum cholesterol levels in patients with panic disorder than controls (12,13). Both of these studies found that patients with major depression did not have elevated cholesterol.

Several epidemiologic studies of psychological correlates of elevated serum cholesterol have been completed. Over 3000 men serving in the U.S. Army completed psychiatric inventories and had serum lipid determinations (14). Men with generalized anxiety disorder had cholesterol levels that were 5 mg/dL higher than men without generalized anxiety disorder. Of note in this study, antisocial personality disorder was associated with cholesterol levels that were 7 mg/dL lower than those without antisocial personality. This association may be related to higher levels of alcohol consumption in antisocial personality disorder. Total cholesterol levels were not associated with major depression. No association was found between psychiatric diagnosis and HDL-cholesterol level or triglyceride level.

A British study examined both male and female civil servants for a relationship between the General Health Questionnaire (GHQ) and total serum cholesterol (15). Using logistic regression analysis, psychiatric illness produced an OR of 2:0 for high serum cholesterol (highest serum cholesterol quartile vs lowest serum cholesterol quartile).

In summary, there is epidemiologic and clinical evidence that psychiatric disorders may contribute to the risk for hypertension, nicotine dependence and elevated serum cholesterol. These associations may explain some of the studies documenting higher rates of natural death among patient with psychiatric disorders. We will now review some of the effects of psychiatric disorders on mortality in cardiac disease.

Review of Mortality Studies in Psychiatric Illness

Outcome studies of psychiatric populations have documented increased rates of death from natural and unnatural causes. One of the earliest studies of the adverse effect of major depression on cardiac outcome was completed by Carney et al. at Washington University School of Medicine (16). Fifty two patients were administered a structured psychiatric interview prior to cardiac catheterization. In a 1-year follow-up study, presence of major depression was the strongest predictor of major cardiac events. The predictive effect appeared independent of severy of coronary disease, left ventricular function or smoking status.

Of particular interest are recent studies by Frasure–Smith and colleagues (17,18). In these studies, 6-month and 18-month outcomes were examined in a series of patients with myocardial infarction. Two hundred and twenty two patients with acute myocardial infarction were interviewed for depression. The interviews occurred between 5 and 15 days following the acute event and included the National Institute of Health Diagnostic Interview Schedule (19) for major depressive disorder. Subjects in this study also completed the Beck Depression Inventory (BDI; Reference 20) as a measure of depressive symptomatology. Thirty five patients met DSM-III-R criteria for depression (16%). Sixty-eight patients had BDI scores that were 10 or greater (33%), consistent with mild to moderate symptoms of depression.

There were 12 deaths during the 6 month followup period and 21 deaths during the 18-month follow-up period. Presence of major depression increased risk for death during the follow-up period (6-month hazard ratio = 5:74, 18-month hazard ratio = 3:12). Elevated BDI scores were also associated with 18-month cardiac mortality (OR = 7:82). Depression status as measured by the BDI appeared to interact with frequency of premature ventricular contractions (PVCs). Subjects with 10 or more PVCs per h and a score of 10 or more on the BDI appeared most likely to die (OR = 29:1).

Frasure–Smith and colleagues extended their study of depression and cardiac mortality by completing an intervention trial (21). A randomised controlled trial of a psychosocial nursing intervention for depressed patients following myocardial infarction has been completed in a series of 1376 post-MI patients. Men and women were screened monthly for evidence of psychosocial distress (depression and anxiety). Those who demonstrated distress were randomly provided either supportive therapy or intensive educational home nursing interventions. The intervention program did not have any overall effect on survival. Contrary to the study hypothesis, women who received the intervention actually had higher mortality that those who did not receive the intervention.

There is limited study of the effect of antidepressant therapy or electroconvulsive therapy on cardiac mortality. One naturalistic study of 519 depressed patients suggested that inadequate treatment of depression is associated with increased risk for death by myocardial infarction (22). In this study, depressed patients admitted to a psychiatric hospital were grouped into those that received electroconvulsive therapy, adequate antidepressant therapy, inadequate antidepressant therapy and a group that received neither ECT or antidepressant therapy. Electroconvulsive therapy was associated with the lowest mortality in a three-year followup period.

What are the potential mechanisms for major depression to influence the outcome of those with coronary artery disease? It is known that mental stress can induce myocardial ischemia during daily activities. Gullette (23) and colleagues studied the effects of negative emotions on myocardial ischemia. A series of patients completed self-report measures of activities and emotions during 48 h of ambulatory ECG monitoring. The frequency of episodes of myocardial ischemia during the hour after negative emotional responses was compared with the frequency of ischemia during time without negative emotions. The risk ratio for myocardial ischemia and negative emotions was 3:0 for "tension," 2:9 for "sadness," and 2:6 for "frustration." One would expect that major depression is likely to increase the amount of time that an individual experiences tension, sadness, and depression and hence increase the duration and perhaps severity of myocardial ischemia.

Another potential mechanism for the depression and mortality linkage would be an association between depression and reduced heart rate variability, another factor found to be associated with mortality. Carney et al. (24) studied the association of depression with reduced heart rate variability in a series of patients with coronary artery disease. Decreased heart rate variability was found to be an independent risk factor for mortality in cardiac disease populations. Depressed patients with coronary artery disease demonstrated reduced heart rate variability in this small sample size series of 19 patients. The exact mechanism for a relationship between depression and reduced heart rate variability is unknown.

Potential mechanisms explaining the association of depression with cardiac mortality could include: altered noradrenergic status or increased risk for cardiac arrhythmias. The previously mentioned studies by Frasure–Smith et al., would support an arrhythmia-related mechanism as the potential cause.

A not uncommon mechanism is iatrogenic. Antidepressant medications are known to produce arrhythmias, reduce cardiac performance and cause postural hypotension if used early (within 6 weeks) in the recovery phase after infarction.

Is Cholesterol Lowering Associated with Suicide?

Two large clinical trials for the drug treatment of hyperlipidemia [The Helsinki Heart Study (25) and the Lipid Research Clinics Primary Prevention Trial (26)] reported higher rates of deaths due to homicide, suicide, and accidents in the groups receiving cholesterol-lowering agents compared to those groups receiving placebo. These findings have set off a flurry of interest in the possible relationship between low serum cholesterol (or decreasing cholesterol levels) and accidental deaths. Possible links between low cholesterol and suicide have received the most attention.

In addition to the prospective trial data, research studies have focused on clinical populations of those with psychiatric disorder and those with suicide attempts. Several studies have demonstrated a link between suicide attempts and low serum cholesterol. A series of psychiatric inpatients were studied to examine the association between low cholesterol and past history of suicide attempts. Six hundred and fifty patients were assessed by a semi-structured interview (27). Serum cholesterol levels were grouped according to quartiles in this psychiatric population. Men with the highest quartile cholesterol level reported fewer suicide attempts than men with the lowest quartile cholesterol values. This finding related to serious suicide attempts, i.e., those with significant medical injury. Age, weight, race, socioeconomic status, alcohol use, and depression were controlled in this analysis.

Two studies focused on cholesterol levels in patients seen in an emergency setting for a suicide attempt. An Italian case-control study measured cholesterol levels in 331 emergency room patients following a suicide attempt (28). Lower serum cholesterol levels were seen compared to controls for both men and women with suicide attempts. Another study compared serum cholesterol in 99 patients following a suicide attempt compared to a group of nonsuicidal psychiatric controls and a group of psychiatrically normal individuals (29). Serum cholesterol levels were found to be low in this study also. A significant lowering was noted for suicide attempters with a diagnosis of mood disorder, personality disorder or neurotic disorder. Of note, no relationship was found for patients with schizophrenia who attempted suicide.

A French study examined the effect of serial serum cholesterol measures on mortality (30). Over 6000 men were followed for a period of 17 years and had serial cholesterol levels during the followup period. Thirty two men completed suicide during the followup period. Suicide associated with low serum cholesterol and also decreasing serum cholesterol during the study period. However, the odds ratio for completed suicide and decreasing cholesterol level was estimated to be relatively low and did not reach statistical significance (OR = 2:17; 95% CI = 0:97–4:84).

These early studies of a possible link between low cholesterol and suicide spawned speculation about potential mechanisms for such an interaction.

Table 1. Guidelines for Treatment of Hypercholesterolemia

CHD risk factors	No Coronary Heart Disease		Coronary Heart Disease
	0 or 1	2 or more	
LDL-Cholesterol			
Goal	<160 mg/dL	<130 mg/dL	≤100 mg/dL
Consider initiation of			
Dietary therapy	≥160 mg/dL	≥130 mg/dL	>100 mg/dL
Drug therapy	≥190 mg/dL	≥160 mg/dL	≥130 mg/dL

Adapted from the U.S. Preventive Services Task Force Recommendations.

Engleberg proposed a relationship between low cholesterol and reduced serotonin receptor in the brain (31). Increases in cholesterol result in an increase in the number of serotonin receptors in the brain of mice. A reduction in serum cholesterol, may produce decreased serotonin receptor density in brain synaptosome resulting in a "poorer suppression of aggressive behavior". An alternate hypothesis has been proposed by Penttinen who has theorized a possible relationship between interleukin-2, lipid metabolism, atherosclerosis and depression (32).

However, there have been several well-designed studies that failed to find a link between low cholesterol and suicide. The Honolulu Heart program enrolled over 7000 Japanese-American men in a prospective study of mortality (33). After 23 years of follow-up, there had been 75 traumatic fatalities and 24 deaths by suicide. Suicide was not related to low serum cholesterol. Rather a slight positive correlation was found between suicide and cholesterol levels, with those with higher cholesterol levels demonstrating a slightly higher risk for suicide. Trauma deaths were increased in those men with the highest alcohol consumption but were not related to serum cholesterol levels.

A large Finnish study also failed to confirm a relationship between low cholesterol and violent death (34). A sample of over 20,000 individuals were followed for 10 to 15 years through the use of a death registry. One-hundred ninety-three violent deaths occurred in men and 43 occurred in women. Low serum cholesterol was not associated with violent death when smoking status, systolic blood pressure, alcohol consumption and education were controlled. Interestingly, in this study, smoking was associated with violent death. As expected, frequent alcohol consumption also associated with violent death.

A more detailed review of the accidental deaths in the Helsinki Heart Study and the Lipids Research Clinics Trial has been completed (35). Two homicide deaths that occurred were victims and not offenders with one occuring more than a year after participation in the trials. Of the eight suicides in the trials, five had dropped out of the trials and had not been exposed to cholesterol lowering agents for a significant period of time. Of the accidental deaths in the trials, the majority had another explanation such as a high blood alcohol concentration or pre-existing psychiatric disorder known to be associated with accidental death. The authors of this analysis concluded "little evidence remains to support the hypothesis that cholesterol-lowering drugs are causally associated with deaths due to homicides, suicides, and accidents in these trials."

One potential explanation for some studies finding association between reduced serum cholesterol and suicide could be through a link to a intermediary variable known to increase suicide risk. Low serum levels of cholesterol in the general population do not just include the lower tail of a normal distribution, but also includes those with chronic illnesses. The large Multiple Risk Factor Intervention Trial Research Group studied the relationship of cholesterol to various medical conditions (36). A serum cholesterol below 160 mg/dL was associated with an increased risk of death from liver cancer and pancreatic cancer. It was also associated with cirrhosis, alcohol dependence and suicide. It is possible that the link between low cholesterol and suicide is due to the association between low cholesterol and some chronic medical illnesses or alcohol dependence. Interestingly, high cholesterol levels were associated with illnesses other than those associated with atherosclerosis including: cancers of the lung, lymphatic system, hematopoietic systems and chronic pulmonary disease.

What are the clinical implications for psychiatrists in this area? At this time the data are mixed about the role of low cholesterol in suicidal behavior. It is generally known that a 1% reduction in cholesterol results in a 2% reduction in risk for coronary events (37). This makes the potential benefit for cholesterol lowering greater than any concern about suicidal risk for the vast majority of patients with hypercholesterolemia. For patients with both major depression and hyperlipidemia, the outlook is not quite as clear. No prospective studies exist that monitor the effect of cholesterol lowering in those individuals with an affective disorder. It is probably prudent to treat hypercholesterolemia in depressed patients in the same manner as non-depressed patients are treated. This population should be monitored for changes in mood during the course of treatment with these agents by a professional with expertise in the diagnosis and management of depression.

Reduction of Cardiovascular Risk in Psychiatric Disorders

Psychiatrists need to maintain an awareness of the cardiovascular risk profile for patients. This is particularly true when patients are not being routinely seen by a primary care physician. Guidelines for screening have been published by several groups. One of the most widely used guidelines is the recommendation of the United States Preventive Services Task Force (USPSTF; Reference 38). The Guide to Preventive Services is a comprehensive review of all the current knowledge about screening, health counseling and immunizations. These recommendations will be summarized for cardiovascular disease risk factors.

Table 1 summarizes the target levels and screening recommendations for the major cardiovascular risk factors. Low density lipoprotein (LDL) cholesterol levels have been identified as the best markers for cardiovascular risk. Cholesterol screening is recommended on a 5 year interval basis for men between the ages of 35 and 65 and for women between 45 and 65. More frequent screening and screening at a younger age is indicated for those with a family

Table 2. Adult Target Levels and Screening Recommendations for Cardiovascular Risk Factors

	Target Levels		Screening Age Levels		
	Women	Men	Women	Men	Interval
Cholesterol	see table 1		45–65	35–65	5years
Systolic BP	<140	<140	>20	>20	2 years*
Diastolic BP	<90	<90	>20	>20	2 years*
Height/weight (BMI)	<27.3	<27.8	>20	>20	†
Blood glucose	<140 mg/dL	<140 mg/dL	>20	>20	‡
Daily alcohol (units)	<3	<5	>20	>20	†

* Yearly screening recommended for those with diastolic BP between 85–89 mm Hg.

† Periodic screening recommended without specific interval.

‡ Routine screening only for obese men and women over 40, family history of diabetes, or high-risk ethnic groups (Native Americans, Hispanics, African Americans).

history of hypercholesterolemia. Target levels that indicate a need for intervention are based upon the presence or absence of known coronary heart disease and the number of other cardiovascular risk factors known to be present. More aggressive identification and treatment of hypercholesterolemia is indicated for individuals with documented coronary heart disease and for those with additional cardiovascular risk factor. Dietary therapy is indicated as the first line of intervention followed by drug therapy for those who do not respond to dietary interventions or have higher LDL-cholesterol values.

Target levels for screening and intervention are set for both systolic (140 mm Hg) and diastolic (90 mm Hg) blood pressure. A 2-year interval between screening episodes is generally appropriate for those with a history of normal blood pressure readings. For those with diastolic blood pressures between 85 and 89 mm Hg, it is recommended that screening occur on a yearly basis. Hypertension is not diagnosed on a single blood pressure reading but should be only diagnosed following three separate elevated blood pressure measurements on three separate visits.

Obesity screening is recommended on a regular basis. The body mass index is an appropriate measure of obesity and is defined as the weight in kilograms, divided by the height in meters squared. Initial interventions for obesity should include promotion of physical activity and dietary counseling.

Routine screening for diabetes is not currently recommended in low risk populations. Screening is appropriate for obese men and women over 40, or for high risk ethnic groups such as African Americans, Native Americans, and Hispanics or those with a family history of diabetes. Screening is also appropriate for those with another cardiovascular risk factor to determine the overall risk. Fasting blood glucose levels greater than 140 mg/dL are generally agreed as indicative of diabetes. Recently, this guideline has been modified. Fasting blood levels of 125–140 is now acknowledged as cause for concern and close follow-up (39). More than one elevated result is needed before the diagnosis can be confirmed.

Alcohol consumption may play a role in reducing cardiovascular risk. This possible benefit is limited to a low daily alcohol level, not more than one to two drinks per day. However, all cause mortality is increased for women drinking more than two drinks per day, and men drinking more than 4 drinks per day. One standard drink is defined as 12 ounces of beer, a 5-ounce glass of wine, or 1.5 ounces of distilled spirits. Excessive alcohol intake may also contribute to the risk for hypertension and reduce the effectiveness of interventions aimed at lowering blood pressure.

Summary

High rates of cardiac disease and psychiatric illness in the general population result in a significant number of patients with combined illness. Cardiac and psychiatric disease comorbidity rates are increased by the association of psychiatric illness with increased rates of hypertension and tobacco use. Psychiatrists should be aware of the need for both primary and secondary coronary heart disease prevention among their psychiatric patients. Patients should be encouraged to schedule routine screening examinations with their primary care physicians. For some patients, psychiatrists may want to assume a screening role and evaluate for the presence of significant cardiovascular risk factors. At the present time, psychiatric disorders do not alter the recommendations for preventing heart disease—these recommendations should include reduction of elevated serum cholesterol, normalization of blood pressure, avoidance of nicotine and excess alcohol use, and the development of an active physical lifestyle. Consultation-liaison psychiatrists can provide a resource for identification and intervention for major depression following myocardial infarction.

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