Current PSYCHIATRY

Brain/body connection

Treating depression in patients with cardiovascular disease

Depression often precedes coronary disease by about 30 years—suggesting possible cause and effect.

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Depression can exacerbate cardiovascular disease (CVD), and CVD can exacerbate depression (*Figure*). Thus, effectively treating depression enhances heart disease treatment, particularly if psychiatrists and medical physicians collaborate in providing patient care.

This article describes a patient with risk factors for heart disease, illustrates the physiologic pathways that link depression and CVD, and offers clinical tips to help you improve outcomes for patients with both disorders.

CASE REPORT: TRYING TO 'GET GOING'

Mr. D, age 51, presents with vegetative symptoms and a personal and family history of CVD, depression, and substance abuse disorders. He was born in a small

Figure

Neuroendocrine pathways by which depression may cause or promote CVD

Hypothalamus-pituitary-adrenal (HPA) axis dysregulation in about one-half of patients with major depression

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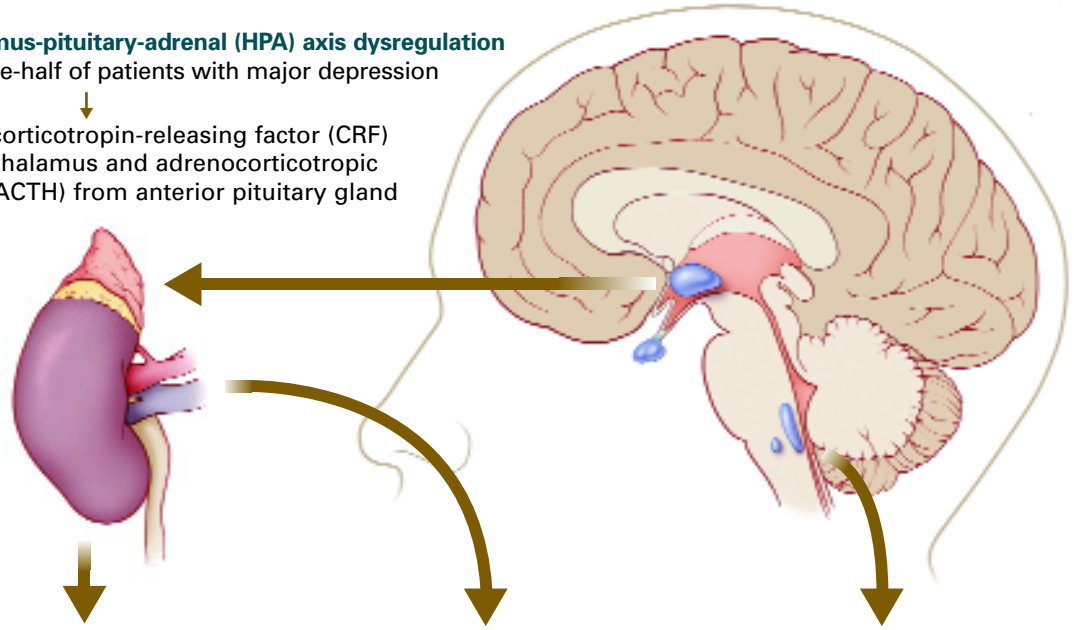
Increased corticotropin-releasing factor (CRF) from hypothalamus and adrenocorticotropic hormone (ACTH) from anterior pituitary gland



Increased catecholamines from adrenal medulla

↓

Decreased eicosanoids
Increased platelet-derived growth factor

↓

Platelet activation

↓

Increased vasoconstriction, atherosclerosis, and thrombus formation

Increased cortisol production by adrenal cortex

↓

Increased visceral fat stores

↓

Increased fatty acids

↓

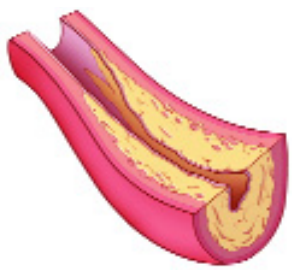
Increased risk of hypertension, glucose dysregulation, and hyperlipidemia

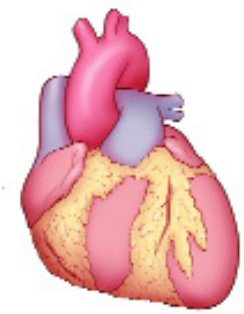
Major depression is associated with chronic:

- **Increased** sympathetic nervous system activity
- **Decreased** parasympathetic nervous system activity

↓

Decreased heart rate variability
Increased blood pressure variability and risk of cardiac arrhythmias





INCREASED RISK OF CARDIOVASCULAR DEATH

ILLUSTRATION BY MARCIA HARTSOCK

Box

The depression-CVD connection

Among patients with a recent myocardial infarction (MI), as many as two-thirds report depressive symptoms.[1] Major depression has been reported in:

- 16% to 22% of patients hospitalized post-MI,[2,3] compared with 5% in the general population and 10% in the primary care population[4]
- 15% of patients with unstable angina[5] and 20% of patients undergoing coronary artery bypass (CABG) surgery.[6]

Among the annual 1.5 million Americans who have an acute MI or unstable angina, 40% develop depression immediately thereafter. These 600,000 depressed patients are three times more likely to die within 6 months, compared with post-MI patients who are not depressed.[7]

town in Kentucky and raised in Louisville's poorest neighborhood. After his mother died at age 42 of "hardening of the arteries," his father started drinking more, working less, and "never really got going again."

Mr. D worked 20 years as a construction contractor, often running several work crews at once. At age 41, he slid into a depressive episode after his second divorce. He struggled with low energy, disturbed sleep, hopelessness, and increased smoking and drinking for 1 year, but he did not seek help.

Two years later, he suffered an inferior wall transmural myocardial infarction. His CVD risk factors included family history of early heart disease, smoking for 32 years, and elevated low-density lipoprotein (LDL) cholesterol. After subsequent episodes of unstable angina, stents were placed in two coronary arteries. Though his cardiologist cleared him to return to work, he felt able to work only part-time and erratically.

During a visit to their family doctor several years later, Mr. D's wife suggested that her husband might be depressed. Reluctantly, Mr. D consulted a psychiatrist.

The psychiatrist diagnosed major depressive disorder and prescribed sertraline, 50 mg/d. Within 2 months, Mr. D's symptoms had dropped by 50% on a symptom severity measure. He did not refill his prescription, however, because of concerns about sexual side effects. Two months later he was hospitalized for another episode of unstable angina. His depression had returned within 1 month of stopping sertraline.

The psychiatrist switched him to citalopram, 20 mg/d, and carefully monitored depressive symptoms, side effects, and medication adherence. Aside from talking with the psychiatrist for a half-hour in his family doctor's office every few weeks, Mr. D refused to undergo psychotherapy. He eventually achieved depression remission with a combination of citalopram, 20 mg/d, and nefazodone, 200 mg/d.

DEPRESSION-CVD CONNECTION

As in Mr. D's case, depression and CVD commonly occur together, often with serious consequences *(Box)*.[1-7] The association between depression and CVD is not limited to depression's effect on existing disease, however. Depression often precedes coronary disease by about 30 years—suggesting possible cause and effect. Two systematic reviews[8,9] found that depression increased CVD risk by 64%.

Seven well-controlled studies[5-7,10-13] compared the relative effect of depression on the cardiovascular system with that of established CVD predictors. All seven found depression's independent effect to be significant and comparable to or greater than that of ejection fraction, previous MI history, or number of vessels with >50% narrowing.

Comorbid depression and CVD usually persists months or years,[14] and most studies indicate a dose-response relationship; the more severe the depression, the greater the risk for CVD to develop or progress.[8,15]

The link between depression treatment and CVD risk has not been well-studied. The only randomized, controlled trial found that cognitive therapy for depression did not significantly reduce cardiac events among patients with known CVD.[16]

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POSSIBLE MECHANISMS

Depression's effect on CVD. How does depression affect CVD development and progression? Both behavioral and biological pathways may be involved.[17] The behavioral pathway proposes that depression triggers behaviors—such as smoking, overeating, and sedentary lifestyles—that increase the risk of developing or worsening CVD. The biological pathway proposes that neuroendocrine changes during depression accelerate CVD development.

About one-half of persons with major depression exhibit hypothalamic-pituitary-adrenal (HPA) axis dysregulation, with excessive secretion of corticotropin releasing factor (CRF) and chronically elevated cortisol.[18] This HPA dysregulation is related to defective negative feedback at the paraventricular nucleus of the hypothalamus. Chronic HPA axis dysregulation promotes vascular inflammation, and several studies have reported C-reactive protein elevation and cytokine changes in patients with major depression.[19,20]

Major depression is also associated with excessive sympathetic and diminished parasympathetic nervous system activity, potentially contributing to hypertension, increased resting heart rate, decreased heart rate variability, and altered endothelial function.[2,21,22] Each of these factors facilitates arterial plaque formation.

Depression may also exacerbate chronic anxiety and other forms of distress. The combined effects of an overtaxed central nervous system, neuroendocrine dysregulation, and unhealthy behaviors may eventually overwhelm the cardiovascular system.

CVD's effect on depression. How does CVD contribute to depression? The vascular depression hypothesis[23] proposes that diffuse heart and brain atherosclerosis restricts perfusion of limbic and cortical structures that regulate mood. A first depressive episode after acute MI or CABG probably represents exacerbation of cerebrovascular insufficiency that preceded the coronary event.

Table

Four keys to effectively treat depression in patients with heart disease

- **Monitor** depressive symptom severity
- **Provide** adequate trials of SSRIs to maximum tolerable dosages before switching to another agent
- **Combine** medications and psychotherapy whenever possible
- **Collaborate** closely with the primary care physician

In practical terms, this means that pathways linking depression and heart disease include not only biological factors but also:

- psychological factors such as depression, anxiety, and chronic stress
- behavioral factors such as smoking, physical inactivity, and high-fat diet.

HOW TO IMPROVE OUTCOMES

Patients with CVD commonly do not receive effective depression treatment:

- Internists and family physicians give preferential attention to physical illness.
- Patients may have insufficient access to mental health specialists.
- Physicians do not adequately monitor depression treatment.
- Patients are reluctant to accept the stigma of mental illness.

By collaborating with primary care physicians, you can improve the likelihood that depression treatment will achieve remission and prevent relapse *(Table)*.

Risk factors for CVD. Depression contributes to heart disease by exacerbating four major CVD risk factors—smoking, diabetes, obesity, and physical inactivity. By effectively treating depression, you may help patients avoid common depressive symptoms—such as overeating and

sedentary behaviors—that are related to low energy or fatigue.

Educate middle-aged patients with depression about CVD's associated risk. Prochaska's "stages of change" (see *Related resources*) can help them stop smoking, lose weight, and exercise.

Access to cardiac care. Depressed patients may be less motivated than nondepressed patients to pursue cardiac care.[24] Therefore, you may need to:

- encourage your patients to take advantage of indicated state-of-the-art care, including stents, bypass surgery, and medications
- understand patients' complex cardiac regimens and help them adhere when depression interferes with their motivation.

EFFECTIVE DEPRESSION TREATMENT

Patient history. For depressed patients older than 40, take a careful inventory of CVD risk factors:

- family history of heart disease before age 60 for men and age 70 for women
- personal history of smoking, blood pressure >140/90 mm Hg, LDL cholesterol >100 mg/dL, type 2 diabetes, body mass index >30, or physical inactivity (<30 minutes of walking 3 days a week).

In general, the more risk factors, the greater the risk of CVD.

Antidepressant selection. Selective serotonin reuptake inhibitors (SSRIs) are safe and effective for treating major depression in CVD and congestive heart failure.[25] Venlafaxine at doses >300 mg/d may increase blood pressure, so use this drug with caution in depressed patients with hypertension.

No controlled clinical trials have gauged the safety and efficacy of bupropion or mirtazapine in patients with CVD.

Tricyclic antidepressants are contraindicated for 6 months post-MI because they may contribute to arrhythmias. Avoid using them in depressed patients with CVD or conduction defects because of their quinidine-like effects on conduction.

Cardiac medications. Contrary to folk wisdom, beta blockers do not cause depression.[26] Whether or not a patient is depressed, our primary care and cardiology colleagues can use beta blockers to help regulate the peripheral autonomic nervous system, reducing high blood pressure and the risk of arrhythmias.

Make sure warfarin levels are well-monitored when you adjust psychotropic dosages

SSRIs may increase blood levels of beta blockers, warfarin, and other cardiac medications via cytochrome P-450 isoenzyme inhibition. Make sure warfarin levels and other cardiac drug effects are well monitored when you adjust psychotropic dosages.

Divalproex and SSRIs also may reduce platelet aggregation. Patients who are receiving concomitant aspirin or warfarin may bruise or bleed easily and require dosage reductions or medication changes.

Psychotherapy. All patients with major or minor depression and CVD are considered high-risk and are candidates for a trial of brief psychotherapy. Therapeutic goals are to achieve full remission of depressive symptoms as rapidly as possible, prevent relapse, and maximize adherence to cardiac and depression drug regimens.

Collaborate closely with the cardiologist or primary care physician during the patient's depressive episode and occasionally during maintenance treatment. Discuss or share notes on the patient's depressive and cardiac disorders, medication management, symptom monitoring, and behavior changes needed to reduce cardiac risk.

With your added support, patients with depression and CVD are more likely to adhere to antidepressant medications and achieve symptom remission.

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Bottom Line

Collaborate closely with primary care physicians when treating depressed patients with comorbid heart disease. Because depression can exacerbate heart disease, screen midlife and older depressed patients for undiagnosed CVD and cardiac risk factors. Treat depression to remission to help patients adhere to cardiac medications and heart-healthy lifestyles.

Related resources

- National Institute of Mental Health. Depression and heart disease. www.nimh.nih.gov/publicat/depheart.cfm.
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DRUG BRAND NAMES

Bupropion • Wellbutrin
Citalopram • Celexa
Escitalopram • Lexapro
Fluoxetine • Prozac
Fluvoxamine • Luvox
Paroxetine • Paxil
Mirtazapine • Remeron
Nefazodone • Serzone
Sertraline • Zoloft
Venlafaxine • Effexor

DISCLOSURE

Dr. Wulsin is a consultant to Pfizer Inc. and Janssen Pharmaceutica.

Dr. Vieweg is a speaker for Janssen Pharmaceutica, Eli Lilly and Co., Pfizer Inc., Wyeth Pharmaceuticals, Forest Pharmaceuticals, and GlaxoSmithKline.

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