REVIEW

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Heart disease and depression: Don't ignore the relationship

ABSTRACT

Evidence is mounting that depression is a risk factor for the development of cardiovascular disease and portends a worse outcome in cardiac patients. Depression can be easily diagnosed and safely treated in cardiac patients, but it is undertreated.

KEY POINTS

After a myocardial infarction, the incidence of major depression is from 15% to 20%, and an additional 27% of patients develop minor depression.

Depression increases the risk of developing cardiovascular disease. It is also associated with higher rates of cardiac death and all-cause mortality.

Depression may contribute to cardiac disease through an overactive hypothalamic-pituitary-adrenocortical axis, platelet activation, and decreased heart rate variability.

Selective serotonin reuptake inhibitors (SSRIs) are the preferred medications, as they have little effect on blood pressure or cardiac conduction. However, physicians should be aware of significant drug interactions caused by inhibition of cytochrome P450 isoenzymes.

DEPRESSION seems to be a bona fide risk factor for coronary artery disease. Statistical associations exist between depression and the development of coronary disease, and the prognosis is worse for coronary patients with depression. Moreover, there are plausible physiologic mechanisms to explain the link.

Although we do not know if treating depression can improve one's coronary prognosis, it can certainly make the patient feel better. Yet, depression is undertreated in coronary patients.

This paper reviews the surprising association of depression with coronary artery disease and explains the possible mechanisms leading to major adverse cardiac events. It also discusses treatment options, including drug interactions and measures aimed at improving clinical outcomes in cardiac patients.

DEPRESSION IS COMMON

Depression affects 6% of men and 18% of women in the general population at any one time.[1] The lifetime risk is 20% to 25% for women and 7% to 12% for men.[2] In the medically ill, the prevalence of depression can be as high as 40%.[3]

The Global Burden of Disease Study[4] ranked unipolar depression as the fourth leading cause of early death and disability worldwide. In developed countries, only ischemic heart disease confers a higher disease burden than depression.

DEPRESSION AS A RISK FACTOR FOR HEART DISEASE

Cardiovascular disease is the leading cause of death and disability in the United States,[5] and

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TABLE 1

Depression as a risk factor for cardiac disease

AUTHORS	YEAR	NO. OF PATIENTS	FINDINGS*
Frasure-Smith et al[14]	1993	222	Adjusted HR for death: 4.29
Anda et al[9]	1993	2,832	Adjusted RR for cardiac death: 1.5
Ladwig et al[92]	1994	377†	Unadjusted RR for follow-up angina: 3.12
Aromaa et al[93]	1994	5,355	RR for MI in men: 2.62 RR for MI in women: 1.90
Barefoot and Schroll[94]	1996	730	RR for MI: 1.71 RR for death: 1.59
Pratt et al[8]	1996	1,551	OR for MI for history of dysphoria: 2.09 OR for MI for history of major depressive disorder: 4.54
Ford et al[95]	1998	1,190†	RR for CHD: 2.12 RR for MI: 2.12
Ferketich et al[96]	2000	7,893	Adjusted RR for CHD in women: 1.73 Adjusted RR for CHD in men: 1.71 Adjusted RR for CHD death in men: 2.34
Ariyo et al[97]	2000	4,493	Adjusted HR for CHD: 1.15 Adjusted HR for MI: 1.14 (with every 5-unit increase in mean depression score)
Barefoot et al[16]	2000	1,250	69% greater odds of cardiac death 78% greater odds of all-cause death
Penninx et al[18]	2001	2,397	With cardiac disease: RR for cardiac death with major depression: 3.0 RR for cardiac death with minor depression: 1.6
		450	Without cardiac disease: RR for cardiac death with major depression: 3.9 RR for cardiac death with minor depression: 1.5

*HR = hazard ratio, OR = odds ratio, RR = relative risk, CHD = coronary heart disease, MI = myocardial infarction
†All men

Evidence is increasing that depression affects the incidence and outcome of coronary disease

evidence is increasing that depression affects its incidence and outcome (TABLE 1). (Other psychosocial stressors associated with coronary heart disease incidence and worse outcome include anxiety, hostility, hopelessness, social isolation, and lower socioeconomic status.[6])

Incidence of cardiac events increased

Depression is a risk factor for both ischemic heart disease and myocardial infarction (MI).[7] In two studies, subjects with no known cardiovascular disease at baseline were followed for at least 12 years, and both studies reported that a history of depression was associated with an increased risk of both fatal and nonfatal ischemic heart disease.[8,9]

Depression predicts a worse outcome

Depression is associated with a worse prognosis after an MI, whether the depression was evident before the attack or was diagnosed afterwards.

Many patients develop depression after an MI: the incidence of major depression is 15%

Depression and the heart: Pathways of cardiac events

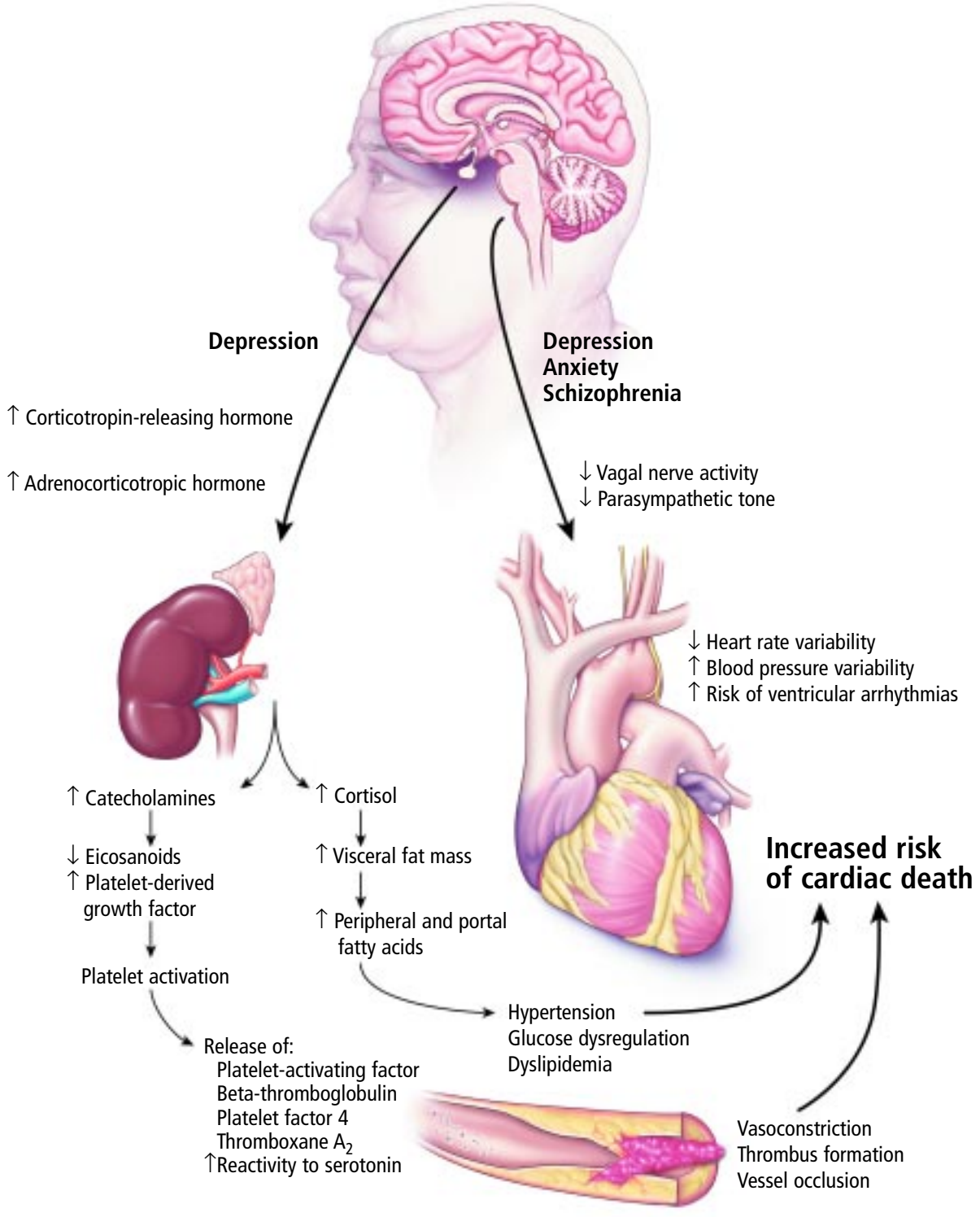

FIGURE 1

to 20%, and an additional 27% of patients develop minor depression.[10–12]

Carney et al[11] reported that major depressive disorder was a better predictor of MI, coronary artery bypass grafting (CABG), angioplasty, or death in the 12 months following cardiac catheterization than was age, New York Heart Association class, cholesterol level, severity of coronary artery disease, left ventricular ejection fraction, smoking, sex, hypertension, ventricular arrhythmias, diabetes, or the use of beta-blockers, calcium channel blockers, diuretics, or nitroglycerin.

In a 16-year prospective study, those who were depressed at baseline had a higher mortality rate compared with nondepressed subjects following a major cardiac event.[13] MI patients were three to four times more likely to die in the subsequent 6 months if they were depressed, as measured 1 week following the MI.[14] In the same study, depression continued to be an independent risk factor for at least 18 months, after controlling for left ventricular dysfunction, prior MI, and age.[15]

Mortality risk seems to be higher for depressed patients in the long term as well. Barefoot and colleagues[16] followed 1,250 patients with coronary artery disease for nearly 20 years after evaluating them with the Zung Self-Rating Depression Scale. Those who were moderately to severely depressed had an 85% greater risk of cardiac death over the next 5 to 10 years compared with nondepressed subjects, and a 72% greater risk of death thereafter.

Mortality risk is higher for depressed patients in the short and long term

Depression affects angina

Depression is also associated with a worse prognosis in patients with unstable angina, the condition that accounts for most coronary hospitalizations.

In a prospective study of 430 patients with unstable angina,[17] depressed patients had a fourfold higher risk of cardiac death or nonfatal MI at 1 year. Depression was an important risk factor even after controlling for left ventricular function, extent of atherosclerosis, and baseline evidence of ischemia on electrocardiography.

Risk increases with depression severity

The more severe the depression, the greater the risk of death following a cardiac event.[8,16–18]

Penninx et al,[18] in a 4-year study of 2,847 men and women, found that the risk for cardiac mortality increased with the severity of depression. Subjects with major depression and no known cardiac disease were nearly four times more likely to suffer cardiac death than nondepressed subjects, after adjustment for smoking, body mass index, stroke, diabetes, and cancer. Minor depression was associated with a 1.5 times increased risk.

This study examined cardiac risk in age-matched controls both with and without cardiovascular disease, and depression was associated with increased mortality in both groups.

Frasure-Smith et al[15] detected an association between minor depression after MI and an eightfold increased risk of cardiac death. However, because many patients with minor depression eventually develop major depression, it is unclear whether minor depression by itself poses such a high risk or if it poses a risk only if it worsens.[19]

Depression affects prognosis after cardiac procedures

Depression is common after CABG: one study found that half of patients reported clinically meaningful depression up to 6 months after the procedure.[20]

Scheier et al[21] reported that patients with depressive symptoms had twice the risk of having a major cardiac event in the 6 months following CABG.

Connerney et al[22] found patients with major depression undergoing CABG were more than twice as likely to die or be readmitted for cardiac causes in the year after discharge. Major depression was as strong a predictor of cardiac events as was low ejection fraction.

POSSIBLE MECHANISMS LINKING DEPRESSION WITH HEART DISEASE

A number of mechanisms have been suggested for the cardiovascular vulnerability seen in depression, including excess cortisol, increased platelet activation, and altered autonomic function (FIGURE 1).

Excess cortisol

In depressed patients, the hypothalamic-pituitary-adrenocortical axis may be hyperactive,[23] with increased concentrations of corticotropin-releasing hormone,[24] reduced function of the glucocorticoid receptors,[25] and higher plasma cortisol concentrations after dexamethasone suppression.[26]

Corticosteroids mobilize free fatty acids, causing endothelial inflammation and excessive clotting, and are associated with hypertension, hypercholesterolemia, and glucose dysregulation.[12,27] Increased circulating lipids and endothelial shearing stress can lead to vascular damage and plaque formation.[28]

An active adrenal medulla may produce more of the catecholamines epinephrine and norepinephrine,[29] which can be measured in plasma or as metabolites in the urine.[30,31] Depressed patients undergoing cold or orthostatic challenge have higher levels of plasma norepinephrine than nondepressed subjects.[32,33]

Catecholamines may also enhance platelet activity by inhibiting eicosanoid synthesis and stimulating platelet-derived growth factor formation.[32]

Half of CABG patients reported depression 6 months later

Increased platelet activation

Platelet activation may also lead to vascular damage and plaque formation.[27] Activated platelets release platelet factor 4 (PF-4), beta-thromboglobulin, thromboxane A_2, and platelet-activating factor, which results in thrombosis, vasoconstriction, and vessel occlusion.[24]

Patients with depression have up-regulation of serotonin receptors on platelets and have fewer serotonin transporters.[34] Increased platelet reactivity to serotonin may promote platelet aggregation, coronary vasoconstriction, and progression of coronary artery disease.[35,36]

Altered autonomic function

Patients with depression commonly show decreased variability in their heart rate, which has also been observed in patients with panic disorder and schizophrenia.[37,38] Carney et al[39] found significantly lower measures of heart rate variability in depressed than in nondepressed patients following acute MI.

Heart rate variability is decreased when sympathetic innervation overrides parasympathetic influences via the vagus nerve, due to increased levels of circulating acetylcholine and catecholamines, as well as input from the cortex, brainstem, and hypothalamus.[40–43]

Decreased heart rate variability is associated with an increased risk of ventricular arrhythmias and sudden death.[44] It is also associated with greater variation in blood pressure, which is also more common in depressed patients[45,46] and is another predictor of cardiac events.[47]

We do not know whether depressed patients have an increased incidence of arrhythmias. However, mortality risk with post-MI depression was found to be greatest among patients with at least 10 premature ventricular contractions per hour.[15]

The Cardiac Arrhythmia Pilot Study (CAPS) found that depressive symptoms continued to predict increased cardiac events at 1 year, even after controlling for premature ventricular contractions or episodes of nonsustained ventricular tachycardia.[48]

DIAGNOSING DEPRESSION

Even though depression is common, it often goes undiagnosed and undertreated in medical settings.[49–51]

Many clinicians think that depression after an MI or CABG is merely a transient reaction to the event and does not deserve special attention. But, as we have seen, multiple studies have shown that depression contributes substantially to an increased risk of cardiac mortality. And even if the depression seen in heart disease is situational, its resolution is often prolonged and can be shortened with treatment.[52]

Many patients with heart disease struggle with issues of dependence or loss of self-esteem and sometimes experience fear, frustration, or guilt from having led an illness-promoting lifestyle.

Are symptoms due to depression or medical illness?

Diagnosing depression after a cardiac event is particularly difficult, because many medical patients have somatic symptoms such as

TABLE 2

Diagnostic criteria for depression: Proposed changes for medically ill patients

Must be present

At least 2 weeks of depressed mood OR loss of interest in nearly all activities

Plus additional symptoms*

Significant change in appetite or weight
Insomnia or hypersomnia
Fatigue or loss of energy
Psychomotor agitation or slowing
Feelings of worthlessness or inappropriate guilt
Diminished ability to think or concentrate
Recurrent thoughts of death or suicide

FROM THE AMERICAN PSYCHIATRIC ASSOCIATION: DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS, FOURTH EDITION, TEXT REVISION. WASHINGTON, DC: AMERICAN PSYCHIATRIC ASSOCIATION; 2000.

Proposed modified additional symptom list for the medically ill†

Anhedonia – loss of pleasure/enjoyment
Unusual tearfulness
Depressed appearance
Social withdrawal
Ruminating thoughts
Hopelessness/helplessness
Psychomotor agitation or slowing
Feelings of worthlessness or inappropriate guilt
Diminished ability to think or concentrate
Recurrent thoughts of death or suicide

*A total of five symptoms constitutes major depression; a total of two to four constitutes minor depression.
†Proposed by Cavanaugh[54] and Endicott[52]

fatigue and poor appetite,[53] which are also symptoms of depression.

To address this problem, Endicott,[52] Cavanaugh,[54] and others have proposed additional symptoms to assess depression in the medically ill (TABLE 2).

Tools to aid diagnosis

Various screening tests can help to diagnose depression. The Beck Depression Inventory[55] and the Zung Depression Scale[56] are patient-rated and easily scored.

An alternative is a two-question test advocated by Whooley and Simon[57]:

- In the past month, have you felt "down," depressed, or hopeless?
- In the past month, have you had little pleasure or interest in doing things?

The test is 96% sensitive: almost all who are depressed answer yes to both questions. However, because its specificity is only 57%, the clinician should obtain additional information to substantiate the diagnosis.

Two questions can identify 96% of patients with depression

TREATING DEPRESSION IN CARDIAC PATIENTS

There is no good evidence that treating depression improves cardiac prognosis. Nonetheless, we recommend treating it, even if only to improve mood and quality of life.

Psychotherapy can be tried for mild depression. Only cognitive behavioral therapy and interpersonal psychotherapy have proven effective without medications, though this has not been specifically evaluated in cardiac patients.[58,59] If the patient has not improved after several weeks, medication should be added.

We recommend antidepressant medica-

TABLE 3

Antidepressant medications to avoid in cardiac patients

MEDICATIONS	POTENTIAL DRAWBACKS
Tricyclic antidepressants (Contraindicated in patients with ischemic heart disease)	Tachycardia Prolonged PR, QRS, and QTc intervals Orthostatic hypotension Class 1A antiarrhythmic properties
Monoamine oxidase inhibitors (Avoided unless depression is refractory)	Orthostatic hypotension Dietary restrictions required to prevent hypertensive crises

tion for moderate to severe major depressive disorder. The clinician should see the patient several times over the subsequent 2 months to assess suicide potential and treatment outcome, or to refer the patient to a psychiatrist.

SSRIs HAVE BEST CARDIAC PROFILE

All approved antidepressants are effective, but their safety and tolerability vary.

Tricyclics are contraindicated in patients with ischemic heart disease

Tricyclic antidepressants are contraindicated in patients with ischemic heart disease,[60–64] and monoamine oxidase inhibitors are recommended only for depression refractory to other medications (TABLE 3).

Selective serotonin reuptake inhibitors (SSRIs) are preferred for patients with heart disease, because they have few cardiovascular side effects and can easily be initiated by primary care physicians. All SSRIs are similarly effective in improving depressive symptoms and quality of life.[65]

The commonly used SSRIs—fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), and citalopram (Celexa, Cipramil)—are not known to significantly affect blood pressure or cardiovascular conduction. However, bradycardia can occur, and some cases of syncope have been reported.[66,67]

Fluvoxamine (Luvox), which is especially effective in obsessive-compulsive disorder, has recently been linked to intraventricular cardiac delay and prolonged QTc interval.[68]

Fluoxetine has been studied specifically in patients with cardiovascular disease. Despite fairly large doses (average 60 mg/day), no orthostatic hypotension, arrhythmias, or other cardiac conduction effects were noted, except for a 5-beat/minute decrease in heart rate.[69] Interestingly, improved ejection fraction was observed in patients with diminished ventricular conduction at baseline.

Paroxetine and the tricyclic antidepressant nortriptyline were also studied in patients with heart disease. Neither drug significantly affected blood pressure or conduction intervals, but nortriptyline was associated with other adverse cardiovascular effects.[70]

Sertraline was studied in a preliminary open-label trial in 26 patients with major depression following an MI. Most patients improved over 16 weeks of treatment, with no alterations in blood pressure, ejection fraction, cardiac conduction, or arrhythmias induced.[71]

The multicenter, double-blind, placebo-controlled Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) confirmed sertraline's safety in the treatment of depression in heart patients after an acute event. Nearly 370 depressed patients post-MI or with unstable angina participated in a 2-week placebo run-in before being randomized to sertraline or placebo. Patients with a first episode of major depression improved on sertraline according to the Clinical Global Impression Improvement Scale but not on the Hamilton Depression Inventory. Those with recurrent major depressive disorder improved according to both instruments.[72]

Monitor for SSRI-cardiac drug interactions

SSRIs are not completely benign and commonly have gastrointestinal and sexual side

TABLE 4

Some antidepressant drugs raise the levels of some cardiac drugs by inhibiting their metabolism

DRUGS		INHIBITORY EFFECT ON SPECIFIC CYTOCHROME P450 ENZYMES				
		CYP 1A2	CYP 2C9	CYP 2C19	CYP 2D6	CYP 3A4
Selective serotonin reuptake inhibitors*						
Citalopram	(Celexa, others)	0 to +	0	0	0	0
Fluoxetine	(Prozac)	0 to +	+++	++	++++	++
Fluvoxamine	(Luvox)	++++	+++	++++	+	+++
Paroxetine	(Paxil)	0 to +	0 to +	0 to +	++++	0 to +
Sertraline	(Zoloft)	0 to +	++	+ to ++	++	++ to +++
Other antidepressants*						
Bupropion	(Wellbutrin, others)	0	0	0	0	0
Mirtazapine	(Remeron)	0	0	0	0	0
Nefazodone	(Serzone)	0	0	0	+	++++
Venlafaxine	(Effexor)	0	0	0	+	0
Tricyclic antidepressant*						
Nortriptyline	(Pamelor)	0	0	0	0	0
Future agents*						
Escitalopram		0	0	0	0	0
R-Fluoxetine		?	?	?	?	?
Cardiac medications metabolized by P450 enzymes†		R-Warfarin Verapamil Propranolol	S-Warfarin Propranolol NSAIDs	S-Warfarin Propranolol NSAIDs	Beta-blockers Class 1C anti-arrhythmics‡	Calcium channel blockers§ Statins‖ Steroids Lidocaine Quinidine Losartan

0 insignificant, + mild, ++++ potent
*Compiled from references 98–100
†Compiled from references 75, 101–104
‡Encainide, flecainide, and propafenone
§Diltiazem, disopyramide, amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, and verapamil
‖Atorvastatin, lovastatin, pravastatin, and simvastatin

effects. They also interact with beta-blockers, warfarin, digoxin, and other medications by inhibiting the cytochrome P450 (CYP) isoenzymes (TABLE 4). Overall, their benefits outweigh the risks if they are monitored carefully.

SSRIs may help underlying cardiac disease

Although we primarily treat depression in the post-MI period to improve quality of life, SSRIs may also alter the pathophysiology responsible for the increase in cardiac mortality:

- Fluoxetine has been shown to significantly increase heart rate variability[73,74]
- Paroxetine has been shown to reduce high levels of PF-4 and beta thromboglobulin, which are associated with increased platelet activation.[75]

SECOND-LINE AGENTS

Other pharmacologic agents can be used if SSRIs fail.

Psychostimulants, such as methylpheni-

date (Ritalin), can be used to treat patients who do not improve with SSRIs and who have predominant symptoms of fatigue, apathy, or psychomotor retardation.[76] In medically ill patients, methylphenidate 2.5 mg in the morning and early afternoon can be started and the dosage increased as needed. A total daily dose of 20 mg is typically required.

At typical doses, cardiovascular side effects, including tachycardia, tachypnea, arrhythmias, and either hypertension or hypotension, are unusual but should be looked for. Stimulants may also increase warfarin levels and decrease the effectiveness of adrenergic blocking agents such as prazosin (Minipress), doxazosin (Cardura), and guanethidine (Ismelin).[77]

Bupropion (Amfebutamone, Wellbutrin, Zyban) and venlafaxine (Effexor) have been associated with dose-related blood pressure elevations, although they rarely produce electrocardiographic changes and have not been reported to cause conduction delays or arrhythmias.[78,79] They may be used as second-line agents in patients with well-controlled blood pressure.

Nefazodone (Serzone) may induce orthostatic hypotension and has recently been linked to liver failure.

Never hesitate to ask about thoughts of suicide

OTHER TREATMENT CONSIDERATIONS

Ask about suicide

Clinicians are strongly advised to address expressions of hopelessness, worthlessness, or suicidal ideation. Never hesitate to ask about passive or active thoughts of suicide; it could be life-saving.

Refer severe cases to psychiatrists

Psychiatric referral is critical for patients experiencing treatment-refractory or severe depression with either significant functional disability or suicidal thoughts.

Psychiatrists can fine-tune medications and provide psychotherapy, light therapy, or electroconvulsive therapy (ECT). ECT is generally reserved for patients requiring rapid resolution of symptoms or for whom two or more medications have failed. It is safe for cardiac patients who can tolerate general anesthesia.[80]

Social support is also important

Patients with depression after an MI are at higher risk of poor quality-of-life outcomes than nondepressed patients[81]: they are less likely to return to work in the 6 months after their infarction,[82] they are at increased risk for ensuing disability,[83] they use more medical services,[84] and they are less likely to comply with cardiac medications and lifestyle changes.[85]

Social stress contributes to depression in medically ill patients, and hopelessness is an independent risk factor for lower survival in patients with heart disease.[8,86]

Poor social support correlates with higher morbidity and mortality rates, independent of disease severity, in patients with heart disease,[87–89] especially in younger patients.[90]

The Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial, sponsored by The National Heart, Lung and Blood Institute, is a multicenter collaboration designed to evaluate the effects of psychosocial intervention on cardiovascular morbidity and mortality in post-MI patients displaying clinical depression or having little social support.[91] Patients randomized to the psychosocial intervention receive individual and group cognitive-behavioral therapy. Medications are prescribed for patients with severe depression or those not improving with psychotherapy. Study results have not yet been published.

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