Treatment of Depression in Patients With Heart Disease

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Patients with depression are more likely than patients without depression to develop ischemic heart disease and suffer cardiac-related death. Recent evidence suggests that the association between depression and increased cardiac mortality may in part be due to an increase in platelet activity and an imbalance in sympathetic and parasympathetic activity that makes the patient more susceptible to ventricular fibrillation. Available data suggest that the tricyclic antidepressants (TCAs) may increase the risk of mortality in patients with ischemic heart disease. Three studies with the selective serotonin reuptake inhibitors (SSRIs), including a double-blind, randomized comparison of paroxetine with nortriptyline, support the conclusion that the SSRIs have a relatively benign cardiovascular profile. Therefore, they are preferable to the TCAs for treatment of depression in patients at risk for cardiac events. Additional studies are needed to definitively establish the cardiovascular safety of the SSRIs.

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Treatment of patients with depression and concurrent cardiac disease is a complex clinical problem. The frequent comorbidity of these 2 conditions was once considered coincidental, because a high degree of overlap, particularly in the elderly population, would be expected for these 2 highly prevalent diseases. Subsequently, numerous studies have demonstrated that the comorbidity of these conditions is not due to chance but rather is part of a complex bidirectional relationship that results from multiple physiologic factors.

RELATIONSHIP BETWEEN DEPRESSION AND CARDIAC DEATH

Patients with depression have a higher-than-expected rate of sudden cardiac death. The earliest research, and arguably the most definitive to date on this topic, was published by Malzberg in 1937.[1] Malzberg compared the mortality of patients hospitalized for involutional melancholia versus that of the general population. To control for age, the study evaluated patients by decade of life. Overall, the death rate in patients with melancholia was 6 times higher than the rate found in the general population, and an increase in mortality was a consistent finding across patients aged 40 to 75 years. This increased mortality included a 40% death rate from cardiac disease in melancholic patients, which was 8 times that of the general population. These data remain unique because they preceded the availability of somatic treatments for depression and are therefore indicative of the natural course of the disease.

A number of investigators[2–5] have since confirmed the findings of Malzberg. For example, one European study followed 6000 patients with depression for an average of 5 years and reported that the cardiovascular death rates among males and females were 50% higher than they were in the general population.[3] Although the increased cardiac mortality was believed to reflect a physiologic interaction between depression and cardiac function, as the adverse cardiovascular effects of the TCAs became known, the hypothesis emerged that the heightened risk of cardiac mortality might be due to TCA treatment. Weeke and Vaeth investigated this hypothesis by comparing mortality rates in cohorts of depressed patients before and after the TCAs became available.[6] In fact, the cardiovascular death rate was lower after the TCAs became available, which supported the belief that the increased cardiovascular mortality in patients with depression was a disease interaction and raised the possibility that treatment may actually lower cardiovascular risk. A study reported by Avery and Winokur supported this possibility; they compared the mortality rates among adequately and inadequately treated depressed patients.[7] Mortality rates were lower in adequately treated depressed patients compared with the inadequately treated group.

Another factor that makes the association between depression and cardiac mortality difficult to understand is the observation that patients with depression are more likely to smoke and less likely to succeed in smoking-cessation efforts.[8] Some researchers hypothesized that

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smoking could account for the higher cardiac mortality rates among depressed patients compared with those of the general population. To test this hypothesis, investigators reanalyzed epidemiologic data from 6 studies of mortality rate in depression while controlling for cardiovascular risk factors, including smoking.[9–14] After multiple risk factors were controlled for, data from 5 trials demonstrated a significant increase in symptomatic and fatal ischemic heart disease in patients with depression. For example, among 1198 male medical students followed over a median of 35 years, and after risk factors such as smoking, weight, and family history were controlled for, men with depression were more likely to have a myocardial infarction (MI) than men without depression.[14] Further support for the relationship between depression and cardiac disease resulted from a trial that used the more restrictive DSM-III criteria for the diagnosis of depression. Results showed that patients with depression were 4 times more likely to have an MI than patients without depression even after controlling for known medical risk factors.[12]

THE INTERACTION BETWEEN DEPRESSION AND CARDIAC DISEASE

In a large and well-designed study of 283 post-MI patients, Schleifer and colleagues found an 18% incidence of major depression and a 27% incidence of minor depression, with almost half of the patients with major depression still meeting diagnostic criteria for the condition after 3 months of follow-up.[15] Similar results were noted among 50 patients with documented coronary artery disease, of whom 18% had coexisting major depression (as defined by DSM-III criteria).[16] A study of 222 patients by Frasure-Smith and colleagues demonstrated a significantly higher cardiac death rate following MI in patients with major depression and also in patients with Beck Depression Inventory (BDI) scores ≥ 10 compared with post-MI patients without depressive symptomology.[17] This study is important because it documented that the increased risk of cardiac death is not limited to those with major depression; post-MI patients with depressive symptoms (score on the BDI of 10 or higher) that were not severe enough to meet diagnostic criteria for major depression were also at higher risk of cardiac death compared with post-MI patients with BDI scores lower than 10.

CARDIOVASCULAR EFFECTS OF TRICYCLIC ANTIDEPRESSANTS

Finding a safe and effective treatment for depression in patients with cardiac disease is an important clinical priority. Although the TCAs are highly effective, the risk of Type IA antiarrhythmics in patients with ischemic heart disease makes TCA treatment problematic in many older depressed patients.

Orthostatic Hypotension

The most frequent adverse effect of TCAs is orthostatic hypotension, which occurs in both young and old patients but which has its greatest deleterious effect in elderly patients.[18–20] Orthostatic hypotension can result in falls, leading to fractures and cardiac events, including MI and sudden death. This observation is supported by data documenting a 2-fold increase in hip fractures in patients over the age of 65 years who received TCAs.[21] As reported in clinical trials, the incidence of orthostatic hypotension in patients taking any TCA other than nortriptyline is about 10%.[18,22–24] Nortriptyline is associated with significantly lower incidence of orthostatic hypotension and can be prescribed for patients who cannot tolerate the orthostatic effects of other TCAs.[25,26]

Cardiac Conduction

It is established that the TCAs slow cardiac conduction. According to electrophysiologic studies, these drugs cause an intraventricular (as opposed to atrioventricular) nodal conduction prolongation similar to that caused by quinidine.[27–29] For patients with normal cardiac conduction, this effect of the TCAs, although evident in increasing PR, QRS, and corrected QT intervals, is not clinically significant. However, in patients with conduction disease below the atrioventricular node, such as bundle branch block, TCAs can cause a 2:1 atrioventricular block.[30] Unlike the tricyclic effect on blood pressure, in which nortriptyline appears to be different than the others, all TCAs have the same effect on cardiac conduction.

Antiarrhythmic Properties

Because patients who ingest an overdose of TCAs can develop fatal ventricular arrhythmias, the TCAs originally were considered to be potentially arrhythmogenic, even in healthy patients, and were to be avoided in patients with preexisting cardiac arrhythmias. Subsequently, it became clear that in contrast to overdose, at therapeutic levels, the TCAs have a Type IA antiarrhythmic effect. Although the Type IA antiarrhythmic activity associated with TCAs was seen as a positive effect, data from the Cardiac Arrhythmia Suppression Trials (CAST) have demonstrated that treatment with Type IC or IA antiarrhythmics in post-MI patients actually results in increased mortality.[31,32] Evidence from animal studies suggests that this increase in mortality results from an interaction between the antiarrhythmic drug and ischemic myocardium, resulting in an increased risk of ventricular fibrillation.[33]

CARDIOVASCULAR EFFECTS OF BUPROPION AND SSRIs IN DEPRESSED PATIENTS WITH HEART DISEASE

Bupropion

In a study of 36 patients with depression who had cardiac disease, treatment with bupropion did not affect heart

rate, induce orthostatic hypotension, slow conduction, or demonstrate antiarrhythmic activity, nor did it have an adverse effect on left ventricular function.[34] These results suggest that bupropion may be appropriate for patients with depression who would not be candidates for TCA therapy because of cardiovascular risk. However, because of the small sample size in this study, it is possible that bupropion has cardiovascular effects that were not detected.

Selective Serotonin Reuptake Inhibitors

In the first randomized, controlled trial comparing the cardiovascular safety of an SSRI with that of a TCA, paroxetine was compared with nortriptyline in 81 depressed patients with ischemic heart disease.[35] Treatment with paroxetine did not induce any clinically significant sustained cardiovascular effects, whereas treatment with nortriptyline resulted in the effects typical of a TCA (e.g., increased heart rate, orthostatic hypotension, and antiarrhythmic activity). Most importantly, the rate of serious adverse cardiac events that required discontinuation of medication was significantly higher in the nortriptyline group than in the paroxetine group (17% vs. 2%, respectively).

A second study reported on a 7-week open trial of fluoxetine (mean dose = 55 mg) in 27 patients (mean ± SD age = 73 ± 9 years) with depression (according to DSM-III criteria) and heart failure, conduction disease, and/or ventricular arrhythmias.[36] Fluoxetine significantly reduced mean heart rate by 5 beats per minute and had no effect on blood pressure, cardiac conduction, or ventricular rhythm. A small but statistically significant increase in ejection fraction was observed in patients with left ventricular impairment. Fluoxetine was well tolerated and had fewer adverse effects than a historical comparison group of comparable patients treated with nortriptyline.

The only systematic data available on treatment of post-MI depression is from an open trial of sertraline given to 26 patients 5 to 30 days after MI.[37] Sertraline proved to be an effective antidepressant without significant effect on cardiovascular parameters. Seventy-three percent of patients completed the trial, and there were no serious cardiac events.

The results of these studies support the belief that the SSRIs have a benign cardiovascular safety profile. However, the number of patients who received SSRI therapy in these studies is small (N = 94), so there may be infrequent adverse cardiac effects that these studies did not have the statistical power to detect. Additionally, none of these trials provides data on the cardiac effects of long-term SSRI treatment. Because of the known effects of SSRIs on the cytochrome P450 system, the potential for drug-drug interactions must be considered when prescribing these drugs for cardiac patients who are receiving multiple medications.

CONCLUSION

Patients with depression and coexisting ischemic heart disease are at increased risk for cardiovascular mortality. In these patients, the clinician must weigh the risk:benefit ratio of antidepressant treatment. Available data indicate that SSRIs are safer than the TCAs for the treatment of depression in patients with cardiac disease, although treatment decisions must be carefully individualized, with consideration given to the type and severity of depression and cardiovascular disease and the efficacy and safety profile of antidepressant medications.

Drug names: bupropion (Wellbutrin), fluoxetine (Prozac), nortriptyline (Pamelor and others), paroxetine (Paxil), sertraline (Zoloft).

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