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Depression in coronary artery disease: Does treatment help?

ABSTRACT

Research over the past decade on the link between depression and coronary artery disease (CAD) has moved from establishing the epidemiologic association between depression and CAD to a focus on whether and how treating depression in patients with CAD benefits these patients. Evidence to date indicates that depression therapy does improve depression, albeit somewhat modestly, in CAD patients. The effect of depression therapy on CAD outcomes is less clear, although there is enough positive evidence to encourage further research. The effects of depression treatment on mechanisms mediating increased CAD risk in depressed patients are variable. Future research should perhaps focus on targeting treatment at intermediary mechanisms as well as at depression itself.

Depression's association with incident coronary artery disease (CAD) and recurrent cardiac events became established 10 to 20 years ago. Efforts in the past decade have focused on the specific effects of treating depression in patients with CAD—whether such treatment is beneficial and, if so, exactly how it exerts its benefits. This article briefly surveys the current evidence on these questions after reviewing how we got interested in depression in CAD in the first place.

THE EMERGENCE OF DEPRESSION AS A CARDIAC RISK FACTOR

The shift from a focus on Type A behavior

Not long ago, Type A behavior pattern was the psychosocial variable of greatest research interest as a contributor to CAD. Just 26 years ago, a National Institutes of Health consensus development conference anointed Type A behavior pattern as a CAD risk factor.[1] Five years later, one of the landmark studies in psychosomatic medicine—the Recurrent Coronary Prevention Project—showed that Type A behavior modification, added to usual cardiac care in post–myocardial infarction (MI) patients, not only reduced patients' Type A behavior but also reduced the rate of reinfarction and death.[2]

But that was the high-water mark for Type A behavior in CAD research. The focus soon shifted, especially after the publication of a 1987 review by Booth-Kewley and Friedman showing that larger and later studies found less and less impressive effects of Type A on cardiac outcomes.[3] This same review pointed out the cumulative evidence indicating that depression might be the most important psychological factor associated with coronary disease.[3]

An explosion of research on depression in CAD

In the 10 years following the review by Booth-Kewley and Friedman, there was an explosion of study about depression in CAD.[4] This resulted in what is fair to call a consensus on several key points about this relationship:

- Depression is associated with an approximate 1.5-fold to twofold increase in the risk for incident CAD.[5–8]
- Depression is associated with about a threefold to fourfold increase in the risk of recurrent cardiac events and death in patients with CAD, including patients with a new diagnosis, those with acute coronary events, and those who have undergone revascularization procedures.[9–13]
- Several biobehavioral mechanisms are plausible candidates as mediators of the mind-body relationship linking depression and coronary disease. These include abnormal platelet function, autonomic function, inflammatory processes, and nonadherence to therapy.[4,14]
- Depression is extremely common in CAD, affecting about 15% to 20% of patients, and is a serious illness in its own right, even apart from its effects on cardiac outcomes.[9–11,15–17]

In light of these observations, the obvious research questions are whether treating depression in patients

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with CAD helps, and if so, what it helps with—the depression itself, the pathophysiology and outcomes of CAD, or both. These questions have been the increasing focus of the past 10 years.

DOES DEPRESSION THERAPY IN CAD PATIENTS IMPROVE DEPRESSION IN THESE PATIENTS?

The short answer to this question is an almost unqualified yes. Even setting aside the literature on tricyclic antidepressants (which is an old literature but impressive in its own right in its systematic working through of issues of efficacy and the delineation and management of adverse effects[18–25]), we have at least half a dozen studies showing that depression treatment helps to relieve depression in patients with CAD with reasonable safety and efficacy. Some are open-label, small-scale studies, while others are more rigorously designed and controlled, but the overall conclusion is unambiguous.[26–34]

Roose, Glassman, and colleagues were among the first to describe the effects of antidepressants other than tricyclics in cardiac patients.[26–29] They demonstrated the safety profile of bupropion, but did not report on its efficacy.[26] They demonstrated safety but found rather low efficacy of fluoxetine in doses up to 60 mg/day in markedly depressed inpatients, many of whom had a "melancholic" profile (early-morning waking, positive diurnal mood variation, guilt, anhedonia, poor appetite).[27,28] In a randomized double-blind trial, these same researchers subsequently demonstrated paroxetine to be at least as effective as the tricyclic agent nortriptyline and to have excellent tolerability at doses up to 40 mg/day.[29]

Strik et al published an early study of the efficacy of depression treatment in 54 patients with major depression after a first MI.[30] Fluoxetine demonstrated superiority over placebo with respect to the percentage of patients achieving a clinical response (48% vs 26%; $P = .05$) (clinical response was defined as a $\geq$ 50% reduction in the Hamilton Depression Rating Scale [HAM-D] score), but fluoxetine did not have a statistically significant effect on HAM-D symptom ratings except in the subset of patients with mild symptoms to start with. This is somewhat counterintuitive, and to be contrasted with the results of SADHART.

The Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), conducted in depressed patients following MI or unstable angina, is well known.[31,32] Patients with a recent acute coronary syndrome (acute MI in 74%; unstable angina in 26%) were randomized within 30 days of the coronary event to sertraline or placebo (following a 2-week placebo run-in period for all patients). Sertraline was associated with superior scores on the Clinical Global Impression Improvement Scale, particularly among patients with recurrent depression and more severe depression, but its effect on HAM-D scores was not significantly better than that of placebo. As opposed to the finding of Strik et al, the biggest difference in response was among patients with more severe depression symptoms rather than those with mild symptoms to begin with.

The Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) trial tested the hypothesis that psychosocial intervention aimed at depression and low levels of social support would improve cardiac prognosis in post-MI patients.[33] In this large randomized study (N = 2,481), cognitive behavior therapy exerted a modestly significant effect in reducing symptoms of depression as compared with usual medical care. Most patients in the intervention arm underwent 6 to 10 sessions of individual and/or group therapy over 6 months, and their HAM-D scores improved by approximately 10 points from baseline to 6-month follow-up. However, patients in the usual-care arm also had substantial improvements (almost 9 points) in HAM-D scores at 6-month follow-up.

The Canadian Cardiac Randomized Evalution of Antidepressant and Psychotherapy Efficacy (CREATE) used a 2 × 2 factorial design to assess interpersonal psychotherapy and antidepressant therapy (citalopram) for depression in patients with stable CAD.[34] Citalopram was more effective than placebo in reducing depression symptoms and in achieving response and remission. The mean decline in HAM-D scores was more than 3 points greater in citalopram recipients than in placebo recipients. Interpersonal psychotherapy was no more effective than clinical management.

In none of the studies reviewed above was the benefit of active treatment very powerful—response rates were between 50% and 60%, and remission rates were much lower.

DOES DEPRESSION THERAPY IN CAD PATIENTS IMPROVE CAD OUTCOMES?

In the ENRICHD trial, cognitive behavior therapy–based psychosocial intervention did not result in lower rates of recurrent MI or mortality compared with usual medical care, but the (nonrandomized) use of selective serotonin reuptake inhibitors (SSRIs) by some patients in the study was associated with a 42% reduction in the risk of death.[33,35]

Likewise, depression intervention had no signifi-

cant effect on cardiac outcome in SADHART, although this 369-patient study was not powered to demonstrate such a benefit.[31] Deaths were reduced by more than 50% with sertraline compared with placebo, but there were only 5 and 2 deaths in the placebo and sertraline groups, respectively. The point estimate for sertraline's effect on major adverse cardiac events was a 23% reduction in events (ie, relative risk of 0.77), but the 95% confidence interval corresponding to this relative risk was 0.51 to 1.16, indicating a lack of statistical significance.

Still, this 23% reduction from SADHART was suggestive—certainly enough to interest the cardiologists associated with the study. Together with the ENRICHD trial findings and results from case-control studies indicating that SSRI therapy reduces the risk of incident MI,[36,37] the SADHART findings have encouraged other investigators to suggest additional studies of the effects of antidepressant therapy on CAD outcomes.[38,39]

Notably, in both the ENRICHD trial[40] and SADHART (unpublished data, manuscript in preparation), patients who recovered from depression (regardless of treatment assignment) had better long-term survival, and this was also true in a long-term longitudinal study of patients following coronary artery bypass graft (CABG) surgery.[12] This suggests that interventions to promote recovery from depression should be useful in improving cardiac prognosis, but it does not prove it. It may be that patients whose depression improves are in some way healthier, regardless of their depression intervention.

As noted above, data from observational case-control studies of patients admitted to coronary care units suggest that SSRI therapy reduces incident MI.[36,37] On the other hand, a study of mortality among patients undergoing CABG surgery revealed worse outcomes in those taking SSRIs than in those who were not.[41] Because this study was observational and not randomized, its findings must be interpreted with caution. The effect observed could be due to an adverse effect of SSRI treatment, an adverse effect of depression, or some other mechanism.

DOES DEPRESSION THERAPY HAVE A BENEFICIAL EFFECT ON INTERMEDIARY MECHANISMS LINKING DEPRESSION TO CORONARY EVENTS?

The answer to this question depends on the specific mechanism being considered.

Platelet activation. In the case of platelet activation, the answer may be yes. In a randomized study of depressed patients with ischemic heart disease, paroxetine but not nortriptyline reduced elevated biomarkers of platelet activation.[42] In a substudy of SADHART, blood levels of sertraline and desmethylsertraline were inversely correlated with platelelet activation.[43] Moreover, serotonin reuptake inhibitors appear to reduce platelet activation in proportion to their affinity for the serotonin transporter.[37,44]

Heart rate variability. There is little evidence that depression therapy influences heart rate variability. In SADHART, for instance, sertraline and placebo did not differ in their effects on heart rate variability.[31]

Nonadherence to CAD therapy. It is clear that nonadherence to therapy is more common in depressed patients with cardiac disease than in their nondepressed counterparts[45,46] and that poor adherence is associated with worse cardiac outcomes.[47] But no study in depressed patients has yet demonstrated that depression treatment per se results in improved adherence. One study has demonstrated, however, that adherence tends to "travel with" depression over the course of treatment: as symptoms of depression declined, adherence improved.[48]

FUTURE DIRECTIONS

In the future, a more efficient way to improve cardiac outcomes associated with depression may be to target interventions directly at intermediary mechanisms rather than at depression itself. For example, if depression is robustly associated with a deleterious effect on platelet function that heightens the risk of thrombus formation, it might be helpful to optimize antiplatelet therapy in patients with depression, independent of the depression treatment. Similarly, anti-inflammatory treatments might have added benefit in those cardiac patients who are depressed, because these patients tend to have abnormally elevated inflammatory activity, which is associated with worse outcomes. These hypotheses would need to be specifically tested in randomized controlled trials, of course.

Because depression is associated with smoking, a recent study of a 3-month smoking cessation intervention in patients admitted to a coronary care unit provides an instructive example.[49] At 2-year follow-up, significantly more patients had continuously abstained from smoking in the intervention group than in a usual-care control group (33% vs 9%, respectively), and significantly fewer patients had died in the intervention group compared with the control group (2.8% vs 12%, respectively).

Another desirable objective is the development of treatments that are more robust in their effects on depression for patients with CAD than the interven-

tions tested so far. Higher rates of response and remission of depression would be highly desirable in their own right. Moreover, only with more potent interventions, whose effects separate more robustly from those seen with placebo or usual care, is it likely that depression treatments themselves could affect cardiac outcomes.

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