More Aggressive Treatment for Depression?

TO THE EDITOR: In the April 2009 issue of the *Journal,* Robert M. Carney, Ph.D., and Kenneth E. Freedland, Ph.D. (1) noted that depressed patients in an intervention group who did not experience treatment response had a higher risk of late mortality (which was described as incidence of death ≥6 months following acute myocardial infarction) compared with patients who responded to treatment. The authors pointed out that this relationship was not significant in the usual care arm of the study. They also reported that in the intervention group, there was a lack of improvement, although subjects received 6 months of aggressive treatment. However, only approximately 15% of patients in the usual care group received any form of nonstudy treatment during the first 6 months. Among patients in the usual care arm who did not experience improvement, less than 15% had received any treatment for their depression.

Drs. Carney and Freedland stated that it is not immediately evident why major depression that is not responsive to treatment is associated with a higher risk of cardiac-related mortality and morbidity and concluded that major depression may warrant more aggressive treatment.

It seems to me likely that less improvement of depression would tend to lead to more aggressive treatment. Perhaps, at least in part, the explanation for why the greater risk of cardiac-related morbidity and mortality is "not immediately apparent" is because we do not wish to think that our efforts at treatment, even aggressive treatment, might have harmed our patients. Psychotropic drugs certainly do affect other organ systems—and not always beneficially. A more apt conclusion might be that less aggressive treatment is better, at least with regard to the treatments that were used in the study, while we search for different treatments, a search that the authors rightly advocate.

Reference

1. Carney RM, Freedland KE: Treatment-resistant depression and mortality after acute coronary syndrome. Am J Psychiatry 2009; 166:410–417

JAMES R. NICHOLAS, M.D.
Ely, Minn.

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The Effects of Treatment-Resistant Depression and First-Ever Depression on Mortality Following Acute Coronary Syndrome: Interactive or Independent?

TO THE EDITOR: Drs. Carney and Freedland (1) presented a fascinating review on treatment-resistant depression and mortality following acute coronary syndrome. As a possible mechanism explaining the association between treatment-resistant depression and mortality in acute coronary syndrome patients, the authors suggested the presence of first-ever depressive episodes, which are associated with both treatment resistance and increased risk of cardiac events.

We therefore explored the association between treatment-resistant depression, first-ever depression, and cardiovascular prognosis using data from the Myocardial INfarction and Depression Intervention Trial (MIND-IT), a multi-center randomized controlled trial on the treatment of post-acute coronary syndrome depression. We previously reported (2), using Cox regression analysis, that patients who did not respond to treatment had an unadjusted hazard ratio of 4.89 (95% confidence interval [CI]=1.08–22.10) for new cardiovascular events relative to patients who responded to treatment. Testing the hypothesis of Drs. Carney and Freedland, we adjusted for the presence of first episodes. However, adjusting hardly affected the association (hazard ratio=4.42; 95% CI=0.97–20.10), which is indicative of no support for the hypothesis. An explanation may be that in our sample first episodes were not associated with new cardiovascular events or treatment resistance. However, they are associated with both new cardiovascular events (hazard ratio=4.12 [95% CI=0.53–31.77]) and with treatment resistance (odds ratio=2.57 [95% CI=0.82–8.03]). The number of patients in each subgroup and their associated risk of cardiac events are shown in Table 1.

Our tentative conclusion is that first depressive episodes and treatment resistance are two independent risk factors for worse outcomes that do not interact but add up independently. Our results do not support the hypothesis that first depressive episodes would underlie the association between treatment-resistant depression and negative cardiac outcomes. Since cell numbers in our study were very low, however, we feel that caution is warranted and no firm conclusions can yet be determined.

We agree with Drs. Carney and Freedland that treatment-resistant depression is likely a marker of an underlying cardiac risk factor associated with treatment resistance in patients with coronary heart disease and that researchers should investigate this factor. One possible risk factor that is often overlooked is treatment nonadherence, which is associated with both depression and cardiac prognosis. Treatment nonadherence is one of the reasons for treatment resistance in depressed patients, and it is likely that a patient who is nonadherent to antidepressant treatment is also nonadherent to cardiac aftercare.

References

1. Carney RM, Freedland KE: Treatment-resistant depression and mortality after acute coronary syndrome. Am J Psychiatry 2009; 166:410–417
2. de Jonge P, Honig A, van Melle JP, Schene AH, Kuyper AM, Tulner D, Schins A, Ormel J: Nonresponse to treatment for depression following myocardial infarction: association with subsequent cardiac events. Am J Psychiatry 2007; 164:1371–1378

MARIJ ZUIDERSMA, M.Sc.
Groningen, the Netherlands
PETER DE JONGE, PH.D.
Groningen and Tilburg, the Netherlands

Presented in part at the annual meeting of the European Association for Consultation-Liaison Psychiatry and Psychosomatics (EACLPP), Zaragoza, Spain, June 27, 2008. Drs. Zuidersma

TABLE 1. Patients in Each Subgroup With New Cardiovascular Events

	Group					
	Subjects Responding to Treatment		Subjects Not Responding to Treatment		Total	
Associated Risk Factor	N	%	N	%	N	%
First episode	2/18	11	10/36	28	12/54	22
Recurrent episode	0/9	0	1/7	14	1/16	6
Total	2/27	7	11/43	26	13/70	19

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Drs. Carney and Freedland Reply

TO THE EDITOR: Our review article on treatment-resistant depression and mortality following acute coronary syndrome was intended to inspire new studies and secondary analyses of relevant databases. We are delighted that Drs. Zuidersma and de Jonge have included a secondary analysis of data from the MIND-IT clinical trial to explore a point we raised in our review. However, we respectfully disagree with their statement that we "hypothesized" that the increased risk for cardiac morbidity and mortality in depressed patients with coronary heart disease is a result of the presence of a higher proportion of treatment-resistant cases among patients whose first episode of major depression coincides with an acute coronary syndrome than among those with a recurrent major depressive episode around the time of an acute coronary syndrome. Actually, we noted that we found no relationship between response to treatment and the type of depressive episode (initial versus recurrent) in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) clinical trial. In ENRICHD, patients with *either* treatment-resistant *or* first-episode depression were at higher risk for mortality than those with treatment-responsive or recurrent depression. Because other studies of depression in patients with coronary heart disease have found initial episodes to be less responsive to treatment than recurrent episodes, we suggested that this potential relationship "deserves more careful study" (p. 414).

For this reason, we are pleased that Drs. Zuidersma and de Jonge examined the MIND-IT data to determine whether these subgroups overlap or, as in the ENRICHD trial, whether they were independent risk factors for cardiac events. Even though first depressive episodes were relatively unresponsive to treatment in the MIND-IT study, first episodes of depression and nonresponse to treatment were independently associated with the incidence of cardiac events. The small size of the subgroups precludes strong conclusions, but the goal of the analysis was hypothesis generation.

We also agree with the authors that poor adherence to the depression and cardiac treatment regimens may explain both poor response to antidepressant treatment and a higher incidence of cardiac events. We have previously suggested that poor adherence to the medical treatment regimen is likely to at least partially explain why depression is associated with an increased risk of cardiac events (1), and we agree that it deserves more careful study.

In his letter, Dr. Nicholas suggests that an initially inadequate response may prompt more aggressive depression treatment, which may prove to be harmful for patients with coronary heart disease. Patients who did not respond to treatment in the ENRICHD clinical trial did not receive more sessions of cognitive behavioral therapy than those patients who responded to treatment, but they were more likely to be given an antidepressant. However, treatment with an antidepressant was associated with improved survival in the ENRICHD trial (2). Although it is not known whether the psychotherapy sessions were more stressful or longer for patients who did not respond to treatment, we do not find support for Dr. Nicholas' conjecture in the ENRICHD trial data. Nevertheless, the possibility that initial nonresponse to depression treatment leads to more aggressive treatment, and in turn, to greater cardiac morbidity and mortality, deserves further consideration.

References

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ROBERT M. CARNEY, PH.D.
KENNETH E. FREEDLAND, PH.D.
St. Louis, Mo.

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The Use of Short Half-Life Antidepressants in the Treatment of Bipolar Depression

TO THE EDITOR: In the February 2009 issue of the *Journal*, Mark A. Frye, M.D., et al. (1), and Joseph F. Goldberg, M.D., et al. (2) examined the predictors of treatment-emergent mania and mixed states in depressed bipolar patients. I would encourage both groups of investigators to review their data to examine two variables that have not been reported. The first is the diurnal variation of mood, which I find to be more extreme in patients who have bipolar depression and may be a predictor of a response to a mood stabilizer in unipolar patients. The second variable is the form of antidepressant given to patients. A convention in publishing is to use the generic names of medications, but this does not distinguish among the three preparations of bupropion (immediate release, 12-hour release, and 24-hour release) and two forms of venlafaxine (immediate- and time-release). Although time-release preparations technically have the same half-life of the underlying compound, their sustained presence keeps blood and