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

and de Jonge receive VIDI grant support from the Dutch Medical Research Council (grant # 016.086.397).

This letter (doi: 10.1176/appi.ajp.2009.09040482) was accepted for publication in May 2009.

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

1. Skala JA, Freedland KE, Carney RM: Coronary heart disease and depression: a review of recent mechanistic research. Can J Psychiatry 2006; 51:738–745
2. Taylor CB, Youngblood ME, Veith RC, Carney RM, Burg MM, Kaufmann PG, Shuster J, Mellman T, Blumenthal JA, Krishnan R, Jaffe AS; ENRICHD Investigators: Effects of antidepressant medication on morbidity and mortality in depressed patients after myocardial infarction. Arch Gen Psychiatry 2005; 62:792–798

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

The authors' disclosures accompany the original article.

This letter (doi: 10.1176/appi.ajp.2009.09040482r) was accepted for publication in May 2009.

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

brain levels more constant, resulting in differing side effects and efficacy profiles.

I have found that in bipolar patients with extreme diurnal variation of mood (characterized by severe a.m.-hour depression followed by significant brightening in the evening), the non-time-release preparations of medications, such as bupropion and venlafaxine, given in low doses in the a.m. hours only can be very helpful and less likely to cause manic switching. Conversely, the long-acting preparations of the same medications tend to cause a reversal of diurnal variation, with improvement in the a.m. hours and agitation in the p.m. hours. It might turn out that short half-life reuptake inhibitors have a place in treating bipolar depression. Other relatively short-acting agents, such as atomoxetine, may also fall into this category.

References

1. Frye MA, Helleman G, McElroy SL, Altshuler LL, Black DO, Keck PE Jr, Nolen WA, Kupka R, Leverich GS, Grunze H, Mintz J, Post RM, Suppes T: Correlates of treatment-emergent mania associated with antidepressant treatment in bipolar depression. Am J Psychiatry 2009; 166:164–172
2. Goldberg JF, Perlis RH, Bowden CL, Thase ME, Miklowitz DJ, Marangell LB, Calabrese JR, Nierenberg AA, Sachs GS: Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD. Am J Psychiatry 2009; 166:173–181

NEIL R. LIEBOWITZ, M.D.
Farmington, Conn.

Dr. Liebowitz is Director of the Connecticut Anxiety and Depression Treatment Center; he has received speaker's honoraria from Forest Laboratories.

This letter (doi: 10.1176/appi.ajp.2009.09030331) was accepted for publication in April 2009.

Drs. Frye and Helleman Reply

TO THE EDITOR: Dr. Liebowitz comments on the safety (i.e., reduced switch rate) and effectiveness of morning single-dose immediate-release antidepressant therapy when there is a classic diurnal variation to the bipolar depressive episode. He further states that, conversely, extended-release antidepressant therapy may "tend to cause a reversal of diurnal variation, with improvement in the a.m. hours and agitation in the p.m. hours." We find these observations intriguing and potentially meaningful.

This is not the first examination of diurnal variation and treatment response. We know that the presence of diurnal variation can be predictive of response to sleep deprivation in some but not all studies (1, 2). Second, patients with bipolar I disorder have responded more frequently to sleep deprivation than patients with major depression (3). This may be related to Dr. Liebowitz's observation of more pronounced diurnal variation in bipolar versus unipolar disorder.

Our study design utilized immediate-release antidepressants, and thus we are unable to comment on the potential extended-release liability or the proposed safety of morning-dose immediate-release therapy. However, we have gone back to conduct a secondary post hoc analysis of prevalence rate of diurnal variation to mood at the time of randomization. For this post hoc analysis, we utilized the Inventory of Depressive Symptomatology (4) question 9 rated mood that appeared to be related to the time of day as a score of 2. The rate of diurnal variation to mood was 14/44 (31.8%) in the treatment-emergent mania group, 25/83 (30%) in the antidepressant responder group, and 20/42 (46.5%) in the antidepressant nonresponder group (χ^2=3.49, df=2, p=0.18). Similarly, there was no difference among the three groups pertaining to mood being worse in the morning, afternoon, or evening.

Antidepressant response based on classic or reverse diurnal variation to mood in the context of antidepressant half-life is a very thought-provoking observation and worthy of controlled study.

References

1. Reinink E, Bouhuys N, Wirz-Justice A, van den Hoofdakker R: Prediction of the antidepressant response to total sleep deprivation by diurnal variation of mood. Psychiatry Res 1990; 32: 113–124
2. Fahndrich E: Effects of sleep deprivation on depressed patients of different nosological groups. Psychiatry Res 1981; 5:277–285
3. Szuba MP, Baxter LR, Fairbanks LA, Guze BH, Schwartz JM: Effects of partial sleep deprivation on the diurnal variation of mood and motor activity in major depression. Biol Psychiatry 1991; 30:817–829
4. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH: The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol Med 1996; 26:477–486

MARK A. FRYE, M.D.
GERHARD HELLEMANN, PH.D
Rochester, Minn.

The authors represent the Stanley Foundation Bipolar Collaborative Network.

The authors' disclosures accompany the original article.

This letter (doi: 10.1176/appi.ajp.2009.09030331r) was accepted for publication in April 2009.

Dr. Goldberg Replies

TO THE EDITOR: Dr. Liebowitz offers an interesting anecdotal observation about the potential importance of diurnal variation in bipolar depression and its possible relationship to mood stabilizer response. Unfortunately, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study did not obtain data on this clinical characteristic during depressive episodes. Existing literature on the phenomenology of bipolar depression has not identified diurnal variation as a feature that is more common in bipolar than unipolar depression, in contrast to other constructs such as reversed vegetative signs (1). However, some investigators have hypothesized that diurnal mood variation may reflect disruptions of circadian rhythms in healthy volunteers (2), suggesting a possible role in cyclical or highly recurrent mood disorders.

Dr. Liebowitz also raises the hypothesis that short-acting antidepressant preparations may be less prone than longer-acting formulations to induce affective polarity switch. STEP-BD found no differences in treatment-emergent affective switch in bipolar depressed patients who underwent equipoise randomization to adjunctive bupropion sustained-re-