Heterogeneity of patients with coronary artery disease and distress and the need to identify relevant subtypes (letter)

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Published in:
Archives of General Psychiatry

Heterogeneity of Patients With Coronary Artery Disease and Distress and the Need to Identify Relevant Subtypes

Drs Frasure-Smith and Lespérance[1] showed that in patients with stable coronary artery disease (CAD), major depressive disorder (MDD) and generalized anxiety disorder (GAD) show substantial overlap and both are associated with prospective major adverse coronary events. The self-report screening instruments for depression (Beck Depression Inventory Second Edition) and anxiety (Hospital Anxiety and Depression Scale anxiety subscale) were strongly correlated and their predictive values for the diagnosis of MDD were virtually the same. Drs Frasure-Smith and Lespérance suggest that a distress disorder under which both depression and anxiety would fall would be a more appropriate diagnostic category to be included in *DSM-V*. In general psychiatry, the suggestion of combining MDD and GAD has many advocates but also many opponents, fueled by differences between patients with MDD and GAD in magnetic resonance imaging patterns and response to benzodiazepines.

In patients with CAD, 3 other distinctions of distress may be more relevant, which Drs Frasure-Smith and Lespérance unfortunately failed to discuss. First of all, the increased cardiac risk in post–myocardial infarction (MI) depression appears to be restricted to first-ever (incident) depressions in individuals who have not had depression before.[2-4] This is not the type of depression we often see at psychiatric inpatient or outpatient clinics, where the overwhelming majority of patients consists of those with 1 or more previous episodes. Several studies have reported that only those with a history of depression and/or onset of depression before the MI—the noncardiotoxic subtype of post-MI depression—respond to antidepressive medication.[5,6] A second distinction in distress that appears to be more relevant than the one between anxiety and depression is between somatic and cognitive symptoms of distress. Previous studies reported that only the somatic-affective symptoms of post-MI depression, such as sleeping problems and fatigue, which are far more dominant in patients with CAD than in psychiatric patients with depression,[7] were associated with an increased risk of major adverse coronary events, and not the cognitive symptoms, such as guilt and negative self-view.[8] Third, subtypes of distress based on the persistence of symptoms appear to be of interest, which is evidenced in observational studies[9] as well as in intervention trials, including ENRICHD and MIND-IT.[10,11] These 3 distinctions in distressed CAD are relevant for *DSM-V* as these aspects of distress are differentially related to cardiac prognosis and/or to treatment response, while anxiety and depression do not differ in this respect.

Progress in the effective treatment of distress in patients with CAD will, in our opinion, depend on distinguishing subtypes based on empirically supported distinctions such as those described earlier and developing interventions for these specific subtypes. To suggest that we are currently on the right track in diagnosing and treating distress in patients with CAD is at odds with the available data. The largest randomized controlled trial in psychosomatic medicine, ENRICHD, reported a (significant) relative decrease of only 1.7 points on the Hamilton Rating Scale for Depression after 24 weeks[12] for cognitive behavioral therapy compared with usual care (mostly no treatment). Comparable results have been found in placebo-controlled antidepressant-medication randomized controlled trials evaluating the efficacy of selective serotonin reuptake inhibitors (sertraline hydrochloride, 0.8 point,[5] and citalopram hydrobromide, 3.3 points, after 12 weeks[6]) but also a serotonin norepinephrine reuptake inhibitor (mirtazapine, 2.4 points).[13] The standardized effect sizes of the studies are in the range of 0.1 to 0.3 while for depression in general the standardized effect sizes of antidepressant medication compared with placebo are about 0.4 to 0.8. The findings of these studies are quite homogeneous and together suggest that guideline-based treatment for depression developed in general psychiatry in patients with CAD results in only minor benefits, of which 70% to 90% can be achieved by usual care or placebo. We hope that *DSM-V* will describe clinically meaningful distinctions of distress in patients with CAD, but we doubt whether these distinctions should follow those in general psychiatry.

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Financial Disclosure: None reported.

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In reply

Drs de Jonge and Ormel believe that we should have discussed the importance of first vs recurrent depression, cognitive vs somatic symptoms of depression, and the persistence of symptoms, all topics on which they have written articles. Instead, we reported the data for the primary aims of our study: to determine the relative prognostic importance of the diagnostic categories of MDD and GAD using the best available standardized clinical interview (Structured Clinical Interview for DSM-IV*) and to compare the prognostic importance of self-reports of symptom levels with the diagnostic categories. In doing so, we sought to expand and attempt to replicate our previous work that suggested that elevated depression symptoms after an MI are associated with as great a prognostic risk as the diagnosis of major depression.[1] Unlike most previous studies, including those cited by de Jonge and Ormel, in which patient assessments were made during a hospital admission for an acute MI, the current study sample was patients with CAD whose most recent admission had been at least 2 months earlier. We found that almost all of the risk associated with elevated depression and anxiety symptoms in these patients was accounted for by those meeting* DSM-IV *criteria and that the risks associated with MDD and GAD were equivalent. We feel that this is an important addition to the literature on heart disease and depression because it eliminated the noise created by short-term reactions to the crisis of hospitalization in which anxiety levels are often transiently high, provided data on the type of patient seen most often in the community, and is clinically useful because of the careful application of accepted psychiatric diagnostic criteria.*

We have discussed the distinctions mentioned by Drs de Jonge and Ormel in articles from our previous studies. Drs de Jonge and Ormel appear to be unaware of these results, which differ from their own. In 1996, we reported data from a study of 222 post-MI patients who were assessed during hospitalization using a modified version of the Diagnostic Interview Schedule and observed up to 18 months for cardiac events.[2] We found that depression during hospitalization predicted cardiac events and that the risk was greater in those with a recurrent depression than in those with a first depression. This is the opposite of what was reported by Drs de Jonge and Ormel. Beyond this omission, there are problems with the other literature they chose to substantiate their view. They cite the 1992 Freedland et al article[3] concerning differences between first and recurrent depressions (based on the Diagnostic Interview Schedule) as evidence that it is only first depressions that are "cardiotoxic." However, that article does not provide any data on cardiac events for the 39 patients included and, in fact, says that it would be interesting to look at this issue in a larger study with longitudinal follow-up. The second article they cite[4] measured past depression with one yes/no question about ever having 2 weeks of depressed mood. Current depression was based on the self-report Beck Depression Inventory, not a diagnostic interview. In sum, there is relatively little evidence to support the idea that it is only first episodes of MDD following an MI that are cardiotoxic.

We have also discussed the issue of cognitive vs somatic symptom reports in an earlier study.[5] In an expanded post-MI sample of 896 we found that cognitive and somatic symptom scores based on the Beck Depression Inventory were highly correlated (0.57). However, again our results differed from those described by de Jonge and Ormel. We found that both cognitive and somatic symptoms were significantly related to increased cardiac events over 5 years even after statistical adjustment for age, sex, educational level, daily smoking, previous MI, thrombolytic treatment for the index MI, Q-wave MI, Killip class greater than 1, revascularization at index hospitalization, left ventricular ejection fraction, prescription of hypoglycemic agents (diabetes mellitus), and β-blockers.

While we agree that one way of making greater progress in psychiatric treatment for patients with CAD may "depend on distinguishing subtypes based on empirically supported distinctions," it may also depend on not making unnecessary distinctions. We also differ in the way we define empirical support. The limited existing literature concerned with "subtypes" of depression in patients with CAD is highly heterogeneous in terms of sample size and characteristics, measures used, and approaches to covariate control. Additional carefully done and reported research is needed to inform both diagnosis and treatment.

Finally, we would also like to correct the misperception that "for depression in general the standardized effect sizes of antidepressant medication compared with placebo are

about 0.4 to 0.8," while those for treating depression in cardiac patients are much lower. Recent evidence based on Food and Drug Administration files indicates that selective publication and reporting by pharmaceutical companies has inflated this evidence.[6] *The best estimate for the impact of antidepressants compared with placebo is about 0.3, similar to what was observed in the overall samples for both CREATE*[7] *and SADHART.*[8]

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Financial Disclosure: None reported.

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