HHS Public Access

Author manuscript

J Psychosom Res. Author manuscript; available in PMC 2017 September 01.

Published in final edited form as:

J Psychosom Res. 2016 September ; 88: 36–41. doi:10.1016/j.jpsychores.2016.07.011.

Clinical Predictors of Depression Treatment Outcomes In Patients with Coronary Heart Disease

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Abstract

Objectives—Patients with coronary heart disease (CHD) who respond to treatment for depression are at lower risk of mortality than are nonresponders. This study sought to determine whether variables that have been shown to predict both depression treatment outcomes in psychiatric patients and cardiac events in patients with CHD, also predict poor response to depression treatment in patients with CHD.

Methods—One hundred fifty-seven patients with stable CHD who met the DSM-IV criteria for a major depressive episode were treated with cognitive behavior therapy (CBT) for 16 weeks, either alone or in combination with an antidepressant.

Results—The mean Beck Depression Inventory (BDI-II) score was 30.2 ± 8.5 at baseline and 8.5 ± 7.8 at 16 weeks. Over 50% of the participants were in remission (HAM-D-17 score ≤7) at the end of treatment. Of the hypothesized predictors, severe depression at baseline (p=0.02), stressful life events during the first (p=0.03) and last (p<0.0001) 8 weeks of treatment, and the completion of CBT homework assignments (p=0.001) predicted depression outcomes. History of prior episodes, anxiety symptoms, antidepressant therapy at study enrollment, and medical hospitalizations or emergency department visits during treatment did not predict treatment outcome.

Conclusions—Patients who are under considerable stress do not respond as well to evidence-based treatments for depression as do patients with less stress. If future studies support these findings, more work will be needed to better address stressful life events in patients who may otherwise remain at high risk for mortality and medical morbidity following depression treatment.

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Competing Interest Statement: All authors have completed the Unified Competing Interest form and declare that they have only received support from the National Institutes of Health, USA, for the submitted work. Dr. Carney or a member of his family owns stock in Pfizer, Inc. The other authors report no potential relevant conflicts of interest.

Keywords

Coronary heart disease; major depression; treatment

Depression is a well-established risk factor for mortality in patients with coronary heart disease (CHD). A meta-analysis of 29 studies found depression to be associated with a 2.7 fold increased risk of cardiac-related mortality in the two years following an acute myocardial infarction (MI).[1] A recent scientific advisory statement from the American Heart Association recommended adding depression to the list of acknowledged risk factors for further cardiac morbidity and mortality in survivors of an acute coronary syndrome (ACS).[2]

There have been only a few controlled trials to determine whether treating depression in patients with CHD improves medical outcomes, and they have been limited by small numbers of cardiac endpoints and small differences in depression outcomes between the intervention and control groups.[3-5] These limitations have made it difficult to detect an effect of depression treatment on cardiac morbidity or mortality, and in fact none of the primary analyses have shown an effect. This has led some to question the value of targeting depression to improve cardiac outcomes.[6] However, secondary analyses have found that patients whose depression symptoms significantly improve with treatment have better survival than those whose symptoms show only minimal or no improvement.[7-9] These findings suggest that survival may improve if depression improves. Similar findings have been reported in a non-randomized trial of exercise training and cardiac rehabilitation in post-MI patients[10] and in a non-randomized[11] and a randomized[12] clinical trial of depression interventions for patients with heart failure.

Given the interest in treating depression in cardiac patients, it is surprising that little is known about the psychiatric and psychosocial variables that predict treatment response in these patients. Some of the factors that have predicted poor responses to depression treatment are also associated with an increased risk of cardiac events in patients with CHD. This may help explain why patients with depression that does not respond to treatment are at higher risk for subsequent morbidity and mortality.

We investigated possible biological predictors of depression improvement in this cohort and found that high normal levels of free T4 thyroid hormone predicted poor depression treatment outcome, but elevated markers of inflammation (CRP, TNF, IL-6), poor sleep quality, and low levels of physical activity did not.[13] However, characteristics of the depressive episode and related psychosocial factors also have been shown to predict improvement in depression, and some of these are risk factors for cardiac events. The purpose of this study was to examine whether baseline depression severity[4,14], a history of depressive episodes[4,15-18], comorbid anxiety symptoms[19-22], concurrent medical hospitalizations or emergencies, or stressful life events[23-26], predict a poor response to depression treatment in patients with major depression and stable CHD.

METHODS

Eligibility Screening and Recruitment

Patients were recruited between May 2009 and August 2013 at cardiology offices and diagnostic laboratories affiliated with Washington University School of Medicine and Barnes-Jewish Hospital of St. Louis. Consenting patients with CHD documented by coronary angiography, a history of coronary revascularization, or hospitalization for ACS, completed the Patient Health Questionnaire (PHQ-9).[27] Patients were excluded from the study if they refused to participate or if their physician did not approve enrollment in the study, or if they had significant cognitive impairment, psychotic features, a comorbid psychiatric disorder other than an anxiety disorder, a high risk of suicide, current substance abuse, hospitalization for ACS or coronary artery bypass graft (CABG) surgery within the previous two months, advanced malignancy, or a disability that would affect compliance with the study protocol. Patients who had been taking a therapeutic dose of an FDA-approved selective serotonin reuptake inhibitor (SSRI) antidepressant for at least 30 days were eligible to participate as long as all of the other eligibility criteria were met. Patients who were not excluded and who screened positive for depression on the PHQ-9 (total score ≥10) were scheduled for a structured diagnostic interview. Those who met the DSM-IV criteria for a major depressive episode, scored ≥16 on the Beck Depression Inventory (BDI-II), and gave written informed consent were enrolled. The study was approved by the Human Research Protection Office at Washington University School of Medicine in St. Louis.

Assessments

Depression Interview and Structured Hamilton (DISH)—The DISH[28] was administered to diagnose major depression using the DSM-IV criteria and to measure the severity of depression from an embedded version of the Hamilton Rating Scale for Depression (HAM-D-17). The DISH includes a screen for exclusionary psychiatric conditions, and assesses psychiatric history including previous major depressive episodes and psychiatric treatment. A HAM-D-17 score of ≤7 was used to define depression remission in this study.

Beck Depression Inventory-II (BDI-II)—The 21-item BDI-II was administered to measure the self-reported severity of depression symptoms. The BDI-II was the primary measure of treatment outcome.[29]

Beck Depression Anxiety Inventory (BAI)—The 21-item BAI was administered to assess self-reported severity of anxiety symptoms.[30]

Stressful Life Events Questionnaire (SLEQ)—Based on the work of Caspi and colleagues [31], the SLEQ assesses the occurrence of 14 types of stressful life events including medical illness of the participant or significant other, death of a family member or close friend, financial problems, problems with close interpersonal relationships, loss of a job, changing residence, and other life threatening or otherwise traumatic situations. The participants were asked to report events that had occurred in the 12 months prior to baseline, and during the previous 8 weeks at the 8^{th} and 16^{th} week of the intervention. They were also

asked to rate the severity of perceived stress associated with each event on a four point scale (0=not or only minimally stressful, 3=very stressful). The total stress score at each assessment occasion is the sum of the stress ratings for that period.

Treatment

The study treatment protocol is described in more detail elsewhere.[13] Briefly, participants received up to 12 sessions of CBT over four months. Those who had already been taking a therapeutic dose of an SSRI antidepressant for at least four weeks prior to enrollment were given CBT and asked to remain on this antidepressant for the 16 weeks of the study. Patients who were not taking an antidepressant at enrollment initially received only CBT. However, if their BDI-II score did not improve by 30% or more by the 5th week of treatment, or by 50% or more by the 8th week, they were prescribed 50 mg of sertraline until the end of the 16-week treatment period. Thus, participants received up to two recognized depression treatments during the four-month treatment period. Nonresponse to adequate trials of at least two evidence-based treatments is a common definition of treatment-resistant depression.[32, 33]

Individual CBT was provided in weekly 50- to 60-minute sessions by one of two therapists, a psychiatric social worker and a master's level counseling psychologist, both with extensive training and experience with CBT for depression in patients with CHD.[34, 35] Brief telephone contacts between CBT sessions were also allowed as needed. Each case was reviewed in group supervision meetings held weekly with one of the investigators (KEF) to provide clinical guidance and to assure fidelity to the CBT protocol. The general principles and therapeutic techniques of the intervention were guided by treatment manuals[36, 37], while adapting behavioral activation plans to address medical safety concerns as needed.[38]

Treatment Adherence

Cognitive Behavior Therapy—Patients' attendance (in-person and telephone sessions) and homework completion were recorded for the duration of treatment. CBT homework assignments are described in the treatment manuals. These include rating the mood associated with specific thoughts or activities, identifying and correcting cognitive distortions, applying problem solving techniques learned during sessions, and planning and engaging in pleasant activities.

Medications—Patients were asked to bring their pill bottles to each psychotherapy session and psychiatrist visit and these were counted and recorded by the research nurse. Patients who forgot to bring their bottle or who missed a treatment session were contacted by telephone and asked to count the remaining pills. The percentage of prescribed pills that were taken and the percentage of CBT homework that was completed during the course of treatment were the primary measures of adherence.

Medical Events

Hospitalizations and emergency department visits were monitored and recorded throughout the 16 weeks of the intervention. Participants' medical records were reviewed at the end of the study to confirm the reported events and assure that all events were recorded.

Statistical Analyses

Analysis of covariance (ANCOVA) was used to examine the relationship between post-treatment depression and the hypothesized predictors of treatment response. In order to determine whether these baseline variables predicted change in depression at 16 weeks, post-treatment BDI-II scores were regressed on each variable while controlling for baseline BDI-II scores. The strength of the linear relationship between change in depression and each predictor is presented as an estimated Fisher z-transformed Pearson correlation coefficient with 95% confidence limits, and estimates from dichotomous predictors are reported as group-level means ± SD (95% CI). Residual analyses were performed to ascertain the validity and goodness-of-fit of each model.

Age and antidepressant use at baseline were included in the adjusted models as potential confounders. Medical hospitalizations and emergency department visits occurring during treatment were also included as potential confounders in all of the models except for the analysis of stressful life events, since hospitalizations are themselves stressful events. In addition, anxiolytic use was included in the anxiety model.

Multiple imputation was used to address missing data, including post-treatment BDI-II scores.[39, 40] All analyses were performed on 100 imputed data sets and the resulting model estimates were then combined for statistical inference. All tests were two-tailed with a Type I error rate per comparison of 0.05. SAS 9.3 software (SAS Institute, Inc., Raleigh, NC) was used to conduct all statistical analyses.

RESULTS

Five hundred seventy-one patients with documented CHD were screened for eligibility. Of these, 157 (27%) had major depression, met all study criteria, and provided written informed consent. Of the enrolled participants, 126 (80%) completed all requirements of the study including the recommended number of CBT sessions and all post-treatment assessments. Those who did not complete all study requirements were less likely to have finished high school (80% vs. 96%; p=0.002) and to be Caucasian (70% vs. 85%; p=0.05), and more likely to have a history of heart failure (37% vs. 19%; p=0.04) than the completers. There were no other differences in any other baseline demographic, medical, or depression variable.

The BDI-II baseline score for the total sample was 30.2 ± 8.5, and the imputed mean post-treatment score was 8.5 ± 7.8. Fifty-two percent of the patients achieved depression remission (HAM-D≤7) by the end of treatment. For the 126 who completed the intervention and all post-treatment assessments, the mean baseline BDI-II was 30.0 ± 8.6, and the mean post-treatment score was 8.3 ± 7.5. Seventy-seven (49%) of the participants were taking an antidepressant at enrollment, and 24 (15.3%) received an antidepressant during the intervention. Medication regimens were stable in most cases during the intervention; 96% of the participants received the same medications throughout the trial.

Table 1 presents the baseline demographic and medical characteristics for the total sample, and for subgroups defined by remission status. These data were previously reported.[13]

There were no significant differences between the remitters and nonremitters on any of the characteristics that were assessed, including baseline antidepressant use.

Table 2 presents the hypothesized clinical predictors of depression treatment response. The table includes the partial correlation and estimated mean for each factor, as well as post-treatment BDI-II scores adjusted for baseline BDI-II and pre-specified covariates. The baseline severity of depression as assessed by the BDI-II predicted post-treatment BDI-II scores (p=0.02). There was no relationship between post-treatment BDI-II scores and pretreatment anxiety symptoms as measured by the BAI (p=0.70). Post-treatment BDI-II scores did not differ between participants who were being treated for an initial vs. a recurrent episode of major depression (p=0.56). The unadjusted and the completers' analyses of these variables yielded similar results.

The self-reported frequency and severity of stressful life events during the 12 months prior to baseline did not predict post-treatment depression scores (p=0.81). However, the stressors experienced during the first (p=0.03) and the last (<0.0001) 8 weeks of the intervention were predictive, with higher stress scores predicting higher post-treatment depression scores. On the other hand, post-treatment BDI-II scores did not differ between participants who were hospitalized or seen at emergency departments during the intervention period and those who were not. The most commonly reported stressors during the 12 months prior to study enrollment were financial problems and interpersonal conflicts, both of which were reported by 59% of the participants. Other frequently-reported stressors included physical illness (56%) and illness of a family member (39%). Financial problems were the only stressors reported at baseline that were associated with depression outcome (p=0.04). During the 16 weeks of the intervention, 31% reported having financial problems, 36% reported interpersonal problems, and 22% reported physical illness as a source of stress. Having financial problems during the intervention was again the stressor most strongly predictive of depression outcome.

The percentage of completed CBT homework assignments was a significant predictor (p=0.001). Although mean adherence to the antidepressant regimen was relatively high (95%), it also tended to predict post-treatment depression scores among patients who were taking an antidepressant (p=0.08).

DISCUSSION

Clinical trials have found that patients with CHD who have a poor response to standard depression treatments experience higher rates of cardiac morbidity and mortality than those whose depression symptoms improve.[7-12] Little is known about predictors of response to depression treatment in patients with CHD. In this study, the pre-treatment severity of depression predicted post-treatment BDI-II scores, suggesting that severe depression in patients with CHD may be less responsive than mild-to-moderate depression to standard therapies. Although more severe depression has been shown to have a more favorable response to antidepressants when compared to placebo, it tends to show less absolute improvement than milder forms[4], and has been associated with a greater risk for mortality

in patients with CHD. [4, 14] Neither anxiety symptoms nor history of depressive episodes (first vs. recurrent) predicted BDI-II scores after 16 weeks of depression treatment.

Stressful life events in the 12 months prior to the intervention did not predict post-treatment depression scores, but being under stress during the intervention was predictive. Notably, hospitalizations and emergency department visits occurring during the intervention period were not predictive. This suggests that it is unlikely that poor response to depression treatment was due to a worsening of cardiac disease.

The potential for an interaction between depression and stressful life events to produce an increased risk for cardiac events has been described in the literature.[41, 42] Our study provides evidence that stressors may also diminish the effectiveness of depression treatment, thereby limiting the possibility of reducing this risk. If stress either mediates or moderates the relationship between depression and cardiac events, it might be necessary to address it before or during depression treatment [43, 44]. Problem-solving strategies might be used to reduce the patient's exposure to stressful environments, and coping skills interventions might be used to improve resilience and reduce perceived stress. Augmentation of depression therapies with these stress-oriented approaches might make it possible to improve both depression outcomes and survival.

Having financial problems in the 12 months before and/or during the intervention was the strongest single predictor of depression outcome. This suggests that financial problems may have a greater impact than adverse medical events on depression treatment outcomes in cardiac patients. Depression treatment was provided at no cost to the participants. However, some of the participants had recently lost their jobs, or had been forced to retire or to reduce their work schedule. Despite having Medicare, Medicaid, or other medical insurance coverage, many of the participants acquired debts directly related to their medical bills, and some were in debt as a result of extended unemployment.

The participants in this trial received up to two treatments (i.e., CBT and antidepressant medications) that have been shown to be safe and effective in patients with CHD. The intervention was similar to the one that was used in the ENRICHD clinical trial, which was the first to show a relationship between improvement in depression following treatment and improved survival.[7] Other clinical trials have also shown a relationship between improvement in depression and improvement in survival using different treatments for depression, including CBT, exercise training, sertraline, mirtazapine, and citalopram.[43] Thus, improved survival in treatment responders does not seem to depend on the specific depression treatments that patients receive.[43] Nevertheless, the present study did not address whether depression severity or life stresses during the intervention period predict improvement in depression with a placebo or with treatments other than CBT alone or in combination with an SSRI. This limits the generalizability of the findings to cardiac patients who are treated with these approaches.

Participants were enrolled in this study no sooner than two months after a cardiac event, whereas the ENRICHD and SADHART trials enrolled patients within days or weeks after an event. Thus, unlike many earlier trials, treatment was provided to these patients when they

were medically stable. It is possible that some of the variables, including anxiety and a first vs. recurrent depressive episode, may predict treatment responses in the immediate post-ACS period but not in later phases of recovery or in patients who are more medically stable.

This study has other limitations which should be noted. We previously reported the relationship between specific pre-treatment medical factors, physical activity, sleep quality, and depression outcomes in this patient cohort.[13] Levels of the thyroid hormone free T4 predicted treatment outcomes, but markers of inflammation (CRP, TNF, IL-6), sleep quality, and physical activity level did not. However, there are other potential medical markers including HPA axis dysfunction, and other potential psychosocial factors such as low social support, that were not assessed in this study. Thus, in addition to those reported here, other factors may predict depression treatment response in patients with CHD.

It is possible that some patients who did not respond favourably to treatment would have responded to more sessions of CBT or to higher doses of sertraline. Twenty percent of the participants did not complete the treatment and/or the post-treatment assessments. This is not an unusually high level of attrition for a trial in which the participants were depressed patients with CHD. Nevertheless, more work needs to be done to find ways to retain patients in future trials and in clinical practice. Anxiety was measured by a self-report inventory of anxiety symptoms and not by the diagnosis of anxiety disorders. It is possible that comorbid panic disorder, for example, may predict treatment response whereas symptoms of generalized anxiety do not. Finally, stressful life events questionnaires are vulnerable to misinterpretations and errors in recall, especially for relatively distant events.[45] Furthermore, ratings of the perceived severity of past or present stressful events may be influenced by current mood.

In conclusion, the pre-treatment severity of depression predicted post-treatment depression, whereas symptoms of anxiety and whether the patient had a first or a recurrent depressive episode did not. Stressful life experiences during the intervention period predicted depression outcomes, but, with the exception of financial problems, stressful life events in the 12 months before the intervention began did not. The proportion of completed CBT homework assignments also predicted depression outcomes. Efforts directed toward reducing or helping patients better cope with life stresses, especially financial problems, should be a priority during or before treating depression in patients with CHD. More work is needed to identify factors that may explain both inadequate responses to depression treatment and a higher risk for morbidity and mortality in these patients.

Acknowledgements

This research study was supported by Grant Number R01HL089336 from the National Heart, Lung, and Blood Institute of the National Institutes of Health, Bethesda, Maryland. The authors thank Patricia Herzing, RN; Iris Csik, ACSW; Jessica McDaniel, MA; Carol Sparks, LPN; and Kimberly Metze, BS for their contributions to the study.

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Highlights

1. Cardiac patients who do not respond to depression treatment are at risk for mortality.
2. Patients with major depression and heart disease were treated for depression.
3. Financial and interpersonal stressors during treatment predicted depression outcomes.
4. Medical hospitalizations and medical emergencies did not.
5. Financial and interpersonal stressors should be addressed in depressed cardiac patients.

Table 1

Baseline demographic and medical characteristics for all participants, and by post-treatment remission status (HAM-D≤7)

Characteristics				
	All participants (N=157)	**Nonremitters (N=76)**	**Remitters (N=81)**	**P**
Demographics				
Age (in years)	59.9 ± 8.7	59.6 ± 9.2	60.2 ± 8.2	.68
Gender (female)	62 (39.5)	32 (42.1)	30 (37.0)	.52
Race (Caucasian)	129 (82.2)	60 (79.0)	69 (85.2)	.31
Education (12+ years)	146 (93.0)	70 (92.1)	76 (93.8)	.67
Medical				
History of MI	98 (62.4)	43 (56.6)	55 (67.9)	.14
History of CHF	35 (22.3)	20 (26.3)	15 (18.5)	.24
Diabetes	68 (43.3)	37 (48.7)	31 (38.3)	.19
Hypertension	129 (82.2)	64 (84.2)	65 (80.3)	.52
History of CABG	56 (35.7)	30 (39.5)	26 (32.1)	.34
History of PTCA	117 (74.5)	55 (73.3)	62 (76.5)	.64
Body Mass Index (kg/m^2)	31.7 ± 6.2	31.1 ± 5.3	32.1 ± 6.9	.31
Current Smoker	38 (24.2)	18 (23.7)	20 (24.7)	.88
Medications				
Statin	134 (85.4)	63 (82.9)	71 (87.7)	.40
Nitrate	37 (23.6)	15 (19.7)	22 (27.2)	.27
Beta blocker	129 (82.2)	59 (77.6)	70 (86.4)	.15
Aspirin	146 (93.0)	71 (93.4)	75 (92.6)	.84
Insulin	35 (22.3)	21 (27.6)	14 (17.3)	.12
Anxiolytic	45 (28.7)	22 (29.0)	23 (28.4)	.94
Antidepressant	77 (49.0)	41 (54.0)	36 (44.4)	.23

*Continuous variables are reported as mean ± SD. Categorical variables reported as number and (%) of participants. One way ANOVA and chi-square tests were used to compare groups.

Table 2

Correlations and mean estimates for hypothesized predictors of depression response after 16 weeks of depression treatment

[1] Predictor	[2] Mean ± SD / N (%)	[3] Estimate (95% CI)	P
BDI-II score			
Baseline	30.2 ± 8.5	0.19 (0.03, 0.35)	0.02
Prior depressive episode			
Yes	122 (77.7%)	8.3 ± 7.7 (6.9, 9.7)	0.53
No	35 (22.3%)	9.3 ± 8.1 (6.6, 12.0)	
BAI score			
Baseline	14.5 ± 8.9	0.04 (−0.13, 0.22)	0.61
Stressful life events			
Stressful life events score (SLEQ)			
Baseline (prior 12 months)	8.9 ± 7.0	0.02 (−0.15, 0.20)	0.81
Treatment Weeks 1-8	4.3 ± 4.1	0.19 (0.02, 0.36)	0.03
Treatment Weeks 9-16	3.7 ± 4.0	0.40 (0.24, 0.55)	<0.0001
Medical events during treatment			
Hospitalization			0.40
Yes	32 (20.4)	7.3 ± 9.0 (4.1, 10.4)	
No	125 (79.6)	8.9 ± 8.0 (7.4, 10.3)	
Emergency department visit			0.90
Yes	31 (19.7)	8.7 ± 8.6 (5.7, 11.8)	
No	126 (80.3)	8.5 ± 8.2 (7.0, 9.9)	
Depression Treatment Adherence			
Medication compliance (% of pills removed from container)	97.0 ± 5.5	−0.47 (−0.76, 0.05)	0.08
% CBT homework completed	59.7± 26.8	−0.29 (−0.44, −0.12)	0.001

[1] Depression scores at 16 weeks are regressed on the hypothesized predictor, controlling for age, baseline depression scores and baseline antidepressant use. Cardiac or other medical events occurring during treatment were also included in all models except SLEQ. BAI models were further adjusted for anxiolytic use at baseline.

[2] Summary scores for the continuous predictor variables are reported as mean ± SD. Categorical variables are reported as the number and (%) of participants.

[3] Estimates are presented as partial Fisher z-transformed Pearson correlations for continuous predictors and mean ± SD post treatment BDI-II scores for dichotomous predictors.