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Residual Symptoms Following Treatment for Depression in Patients with Coronary Heart Disease

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Abstract

Objective—Depression is associated with an increased risk of mortality in patients with coronary heart disease (CHD). The risk may be reduced in patients who remit with adequate treatment, but few patients achieve complete remission. The purpose of this study was to identify the symptoms that persist despite aggressive treatment for depression in patients with CHD.

Methods—One hundred twenty-five patients with stable CHD who met the DSM-IV criteria for a moderate-to-severe major depressive episode completed treatment with cognitive behavior therapy (CBT), either alone or combined with an antidepressant, for up to 16 weeks. Depression symptoms were assessed at baseline and after 16 weeks of treatment.

Results—The mean Beck Depression Inventory (BDI-II) scores were 30.0 ± 8.6 at baseline and 8.3 ± 7.5 at 16 weeks. Seventy-seven (61%) of the participants who completed treatment met remission criteria (Hamilton Rating Scale for Depression [HAM-D-17] ≤ 7) at 16 weeks. Loss of energy and fatigue were the most common post-treatment symptoms both in remitters ($N=44$, 57%; $N=34$, 44.2%) and nonremitters ($N=42$, 87.5%; $N=35$, 72.9%). These symptoms were not predicted by baseline depression severity, anxiety, demographic or medical variables including inflammatory markers or cardiac functioning, or by medical events during depression treatment.

Conclusions—Fatigue and loss of energy often persist in patients with CHD even after otherwise successful treatment for major depression. These residual symptoms may increase the risks of relapse and mortality. Development of effective interventions for these persistent symptoms is a priority for future research.

Keywords

Depressive disorder; treatment; residual symptoms

Depression is a well-established risk factor for cardiac morbidity and mortality in patients with coronary heart disease (CHD) (1, 2). Unfortunately, none of the four largest controlled

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depression treatment trials of patients with CHD that evaluated cardiac morbidity and mortality outcomes found effects on event-free survival (3–6). However, secondary analyses performed on three of these trials found a relationship between improvement in depression and cardiac event-free survival (7–9). Because the presence of even one or two depression symptoms may increase the risk for mortality in these patients (10, 11), full remission must be the goal of treatment. Unfortunately, few patients fully remit with standard treatments (12). How to achieve complete remission is one of the most important challenges in this area of research.

In psychiatric patients with major depression, fatigue, loss of energy, and sleep disturbances are some of the most common symptoms of depression before treatment, and among the most common residual symptoms even in patients who meet standard criteria for remission (13–16). In a study of primary care patients, Conradi and colleagues found that fatigue or loss of energy was reported by 90% and sleep problems by 85% of the depressed patients prior to treatment. Fatigue or loss of energy persisted in 35% and disturbed sleep in 39% of the patients who no longer met the DSM criteria for major depression. In contrast, one or both of the two cardinal symptoms of major depression, sadness and loss of interest, was present in only 21% of the patients who achieved full or partial remission (17). This suggests that standard treatments for depression may not be as effective for fatigue, loss of energy, and disturbed sleep as they are for the other the symptoms of depression (15). This is problematic because these residual symptoms are also among the best predictors of relapse and of recurrent depressive episodes (18–21).

An innovative methodology known as network analysis recently has been used to examine interrelationships among symptoms of depression both before and after treatment. Network analysis models depression as a complex system of interacting symptoms (nodes), with each symptom having a unique pattern of relatedness to the others. The analysis also yields several indices of “centrality” that can be used to assess the importance of symptoms according to their degree of connectivity with other symptoms within the network.

Fried and colleagues conducted a network analysis of pretreatment depression symptom data from 3,867 persons with major depression enrolled in the National Institute of Mental Health’s Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (22). They found that loss of energy was slightly more strongly connected to the other depression symptoms than were the cardinal symptoms of sadness and loss of interest. Van Borkulo and colleagues (23) compared the baseline symptom networks of patients whose depression eventually remitted to those whose depression persisted during a two year follow-up. Fatigue/loss of energy was one of two symptoms, the other being feelings of guilt, that was most strongly connected to the other baseline depression symptoms in those patients who remained depressed.

Thus, fatigue and loss of energy are among the most common symptoms in depressed psychiatric patients. When present, they are among the most likely symptoms to persist after treatment, among the most central in relation to the other depression symptoms in those patients whose depression does not remit, and among the best predictors of relapse or recurrence in patients whose depression does remit following treatment. The aims of this

study were to determine whether fatigue and loss of energy are also among the symptoms most likely to persist following treatment in depressed patients with CHD, to investigate the relationships among these and the other depression symptoms before and after treatment, and to determine whether baseline demographic, medical, and clinical characteristics predict patients with vs. without the symptoms of fatigue and loss of energy following depression treatment.

METHODS

The study protocol is described in detail elsewhere (24, 25). Briefly, patients with documented CHD but without significant cognitive impairment or other debilitating psychiatric or medical illnesses who scored ≥ 10 on the PHQ-9 were evaluated for study enrollment between May 2009 and August 2013. Those who met the DSM-IV criteria for a major depressive episode, scored ≥ 16 on the Beck Depression Inventory (BDI-II), and provided written informed consent were enrolled. 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 they met all the other eligibility criteria. The study was approved by the Human Research Protection Office at Washington University School of Medicine in St. Louis.

Self-Report Measures

Depression Interview and Structured Hamilton (DISH)—The DISH (26) structured interview 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 remission.

Beck Depression Inventory-II (BDI-II)—The 21-item BDI-II was the primary outcome measure and was also used to assess the presence and severity of individual depression symptoms at each assessment (27). Cronbach's alpha was 0.81 at baseline and 0.89 at follow-up in our sample.

Beck Depression Anxiety Inventory (BAI)—The 21-item BAI was administered to assess self-reported severity of anxiety symptoms (28). Cronbach's alpha was 0.87 in our sample.

Pittsburgh Sleep Quality Index (PSQI)—The PSQI (29) assesses sleep quality during the past month. The PSQI global score was used as the primary index of sleep quality for this study. Cronbach's alpha was 0.64 in our sample.

International Physical Activity Questionnaire (IPAQ)—The IPAQ (30, 31) is a well validated self-report inventory assessing the duration and level of exertion of work, exercise, leisure time, and normal daily activities performed nearly every day (32). It classifies the patient's usual level of physical activity as low, moderate, or high. Cronbach's alpha was 0.36 in our sample.

Medical Assessments

Major medical comorbidities including diabetes, hypertension, and heart failure were identified from electronic medical records. Blood samples were drawn in the morning by laboratory personnel blinded to subject identifiers, measurement occasion (baseline or post-treatment), depression status, and the results of other assessments. Each participant rested supine on an examination table for 15 minutes before the blood draw. Participants were asked to refrain from caffeine, alcohol, and tobacco for at least 12 hours prior to the examination. Oral temperature was measured before the blood draw and patients with recent infectious diseases or other disorders that could cause a systemic increase in inflammatory markers were identified. Following the blood draw, ambulatory ECG monitors were attached using standard clinical electrode placements.

Inflammatory Blood Markers—High sensitivity CRP measurement was obtained from an enhanced immunonephelometric assay on a BN-II analyzer (Dade Behring; Newark, NJ). This assay can measure CRP levels of less than 1 mg/dL with assay coefficients of variation below 10%. IL-6 and TNF were measured by high sensitivity enzyme-linked immunosorbent assay (ELISA) (Quantikine HS, R&D Systems) according to the manufacturer's specifications. The intra-assay coefficient of variation and lower limit for detection for TNF and IL-6 are 7.8% and 3.6%, and 0.18 and 0.09, respectively.

Thyroid Axis Function—Total thyroxine (T4) and free T4 levels were measured by immunoassay (Microgenics, Inc.) using standard laboratory procedures with assay coefficients of variation below 8%.

Nighttime Heart Rate—Heart rate during self-reported sleep time was derived from ambulatory ECG monitoring.

Treatment

Participants received between 6 and 12 sessions of individual cognitive behavior therapy (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 that 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 up to 100 mg of sertraline per day 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 (33, 34).

CBT was provided in weekly 50- to 60-minute sessions by a psychiatric social worker or a master's level counselor, both with extensive training and experience with CBT for depression in patients with CHD (35, 36). 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 published treatment manuals (37–39).

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

Associations among changes in the residual symptoms and changes in the other depression symptoms from baseline to post-treatment were estimated using Pearson correlations. Analysis of variance and chi-square tests were used to compare patients who reported individual symptoms on both occasions to those who reported a given symptom only at baseline. SAS 9.3 software (SAS Institute, Inc., Raleigh, NC) was used for these analyses.

A reliable imputation model for missing symptom data could not be fitted due to the high ratio of auxiliary variables to participants. Consequently, the analyses of post-treatment residual symptoms are based on the subset of participants with complete data.

A network analysis of the most common depression symptoms was conducted to identify the most important symptoms in the network by plotting the standard centrality indices of node strength, closeness, and “betweenness” (40). Briefly, node strength is the weighted sum of a particular symptom's connectivity with other symptoms, closeness is a weighted average of the shortest path distance between a symptom and all others, and “betweenness” is the number of times a given symptom appears on paths between other symptoms (41). These analyses were performed with the R statistical software package (version 3.3.1) (42). Because statistical tests of centrality differences are not available, the centrality profile graphs of the remitted and nonremitted subgroups were compared.

RESULTS

As reported previously, 571 patients with documented CHD consented to be screened for eligibility for a “study of depression treatment” (24). Of these, 305 patients scored 10 or more on the PHQ-9, and 157 (27%) also met the DSM-IV criteria for a current major depressive episode, met none of the exclusion criteria, and were thus enrolled in the study. Of these, 125 (80%) completed all requirements of the study including the recommended number of CBT sessions and all post-treatment assessments. The noncompleters were less likely to have finished high school (80% vs. 96%; $p=0.002$), less likely to be White (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 differences in any of the other demographic, medical, or depression variables, including the severity of depression at baseline ($p=0.46$), the proportion of patients with prior depressive episodes ($p=0.33$), or the proportion entering the study on an antidepressant ($p=0.77$).

For the 125 who completed the intervention and all post-treatment assessments, none were febrile, and only three had minor cold symptoms. There were no other signs or reports of

infection or illness. The mean baseline BDI-II was 30.0 ± 8.6 , and the mean post-treatment score was 8.3 ± 7.5 . Seventy-seven patients (61.6%) achieved depression remission by the end of treatment. Sixty-two (49.6%) of the participants were taking an antidepressant at enrollment, and the study antidepressant was prescribed during the intervention phase for 23 (18.4%) of the participants.

Table 1 presents the proportion of patients who rated symptoms from the BDI-II as present (item rating = 1) at both baseline and 16 weeks, present at baseline but not at 16 weeks, absent at baseline but present at 16 weeks, and absent on both occasions. Loss of energy and tiredness or fatigue were present in nearly all of the patients at pretreatment, and were the most prevalent residual symptoms after 16 weeks of treatment for those whose depression did not remit (loss of energy 87.5%, mean item rating 1.08 ± 0.58 ; fatigue 72.9%, mean item rating 1.0 ± 0.81). They were also the most prevalent symptoms among those patients whose depression remitted (loss of energy 57.1%, mean item rating 0.58 ± 0.52 ; fatigue 44.2%, mean item rating 0.44 ± 0.50). Sleep and appetite disturbances were the only symptoms that were reported after treatment by more than 5% of the patients who denied these symptoms at baseline. Nearly 40% of all patients denied insomnia at baseline and at 16 weeks, and nearly half denied hypersomnia on both occasions. Of those who reported insomnia at baseline, 67% denied it at 16 weeks. Of those reporting hypersomnia at baseline, 75% denied it at 16 weeks.

Correlations of baseline to post-treatment change scores for fatigue, loss of energy, and the other BDI-II items are reported in Supplemental Table A, Supplemental Digital Content 1. Pre-post change in the severity of loss of energy and fatigue correlated moderately with each other ($r = 0.47$) but not with changes in the somatic symptoms of sleep and appetite disturbance ($r = -0.04$). Table 2 compares patients with loss of energy and fatigue before and after treatment to those who reported the symptom before but not following treatment on the total score for the BDI-II, HAM-D-17, BAI, PSQI, and the IPAQ, and for demographic and medical variables. Participants who reported fatigue on both occasions reported poorer sleep quality and marginally higher levels of FT4 at pretreatment assessment. Smokers were less likely to report fatigue post-treatment than were nonsmokers. There were no other differences between those with and without fatigue or loss of energy at post treatment. Analyses based on continuous item scores (0–3) rather than on categorical (present/absent) data similarly showed no associations with cardiac, inflammation, or thyroid measures except for FT4.

Figure 1 compares the three network centrality measures for the ten most common pre-treatment BDI-II symptoms for both remitters and nonremitters. The standardized measures of centrality are reported as Z scores. Fatigue was the highest in all three centrality measures in the nonremitters. Network diagrams for those with persistent fatigue and those who reported fatigue at baseline but not after treatment are presented as Supplemental Figures A and B in Supplemental Digital Content 2.

DISCUSSION

The most prevalent post-treatment BDI-II symptoms were loss of energy and tiredness or fatigue, followed by loss of pleasure, loss of interest, and difficulty concentrating (Table 1). Although disordered sleep is one of the most common residual symptoms in depressed psychiatric patients following treatment, nearly 40% of the patients in this study denied insomnia at baseline and nearly half denied hypersomnia both before and after treatment. Of those who reported insomnia at baseline, 67% denied it at 16 weeks. Of those reporting hypersomnia at baseline, 75% denied it at 16 weeks.

Despite a relatively truncated range, change in the severity from baseline to post-treatment for loss of energy and fatigue correlated low to moderately with each other and with some of the other common depression symptoms, including loss of interest, irritability, and poor concentration (Supplemental Table A). However, improvement in fatigue or energy loss was not related to improvement in appetite, insomnia, or other sleep symptoms. Overall sleep quality, as measured by the PSQI, was somewhat lower at pretreatment in those who continued to report fatigue, but unrelated to continued loss of energy. Thus, the relationship between disordered sleep and the continued presence of fatigue and loss of energy does not seem to be straightforward and requires further study.

None of the demographic (age, sex) or major medical variables (prior myocardial infarction, heart failure, diabetes, revascularization, inflammatory markers) at baseline differed between patients with or without fatigue and loss of energy at 16 weeks, nor did the baseline total BDI-II or BAI scores. Thus, there was no evidence that the severity of depression, anxiety, or medical illness accounted for the presence of these symptoms following treatment. Hospitalizations and emergency department visits occurring during the 16 weeks of treatment also did not differ between patients who did or did not report these symptoms following treatment, suggesting that their presence was not strongly influenced by concurrent medical events. Patients who reported smoking were less likely to report fatigue after treatment than were nonsmokers. Given the number of analyses that were conducted, this could be a chance finding. It is also possible that the stimulating effects of nicotine, which is thought to be a method of self-medication for some depressed patients, may account for this effect.

Network analysis provides three measures of centrality which quantify how connected each symptom is to the rest, and therefore which symptoms are more likely to have a key role in a depressive episode. Among the nonremitters, fatigue scored the highest out of the ten most common symptoms on all three indices of centrality. In the remitters, loss of energy was the most central. For both groups, fatigue and loss of energy were the most common residual symptoms after treatment. It is not known whether targeting symptoms identified as being the most central in a depressive episode will improve treatment responsiveness or eliminate residual symptoms. Future research should explore this possibility.

Other than a failure to achieve true remission, what is the significance of these residual symptoms in patients with heart disease? Fatigue is one of the best predictors of new and recurrent episodes of depression. For example, the Baltimore ECA follow-up study found

that the occurrence of fatigue during a 13 year period was associated with a 28-fold greater risk of developing major depression than observed in those participants without fatigue (18). Loss of energy/fatigue has also been shown to be associated with significant psychosocial dysfunction. Fried and colleagues, for example, reported that energy loss was one of four symptoms most strongly associated with psychological impairment (43). If fatigue and loss of energy persist following treatment, psychological impairment may remain even after improvement in other symptoms. There is evidence that somatic symptoms are more strongly associated with cardiac morbidity and mortality than are cognitive symptoms of depression (44). One study found fatigue-sadness to be the only depression symptom cluster that individually predicted cardiac events in ACS patients (45). If fatigue and loss of energy are common residual symptoms, these findings may help to explain why it may be difficult to improve survival even after “successful” depression treatment.

Loss of interest or pleasure (anhedonia) was the next most common residual symptom. Anhedonia has been associated with a relatively poor response to depression treatment (46), although it is less commonly reported as a residual symptom in medically well, depressed psychiatric patients compared to either fatigue or problems sleeping. It has long been recognized as a symptom of depression, and it must be present in order to make a DSM diagnosis of major depression if dysphoric mood is absent. However, it has been challenging to study because it is difficult to distinguish between impaired motivation to engage in pleasant activities and an inability to experience pleasure from doing so (47). This may be especially important in cardiac patients, as many report that they no longer engage in certain pleasant activities alone or with others and therefore do not “enjoy things as much as I used to” or they are “less interested in people or things than before” (BDI-II items). On closer inspection we have often found that those who report anhedonia often believe that they are physically incapable of engaging in their favorite activities without experiencing symptoms or increased fatigue. Thus, in some cases, “loss of pleasure” may simply be due to avoidance of potentially pleasurable activities rather than a loss of the ability to experience pleasure. This symptom deserves further study in cardiac patients, especially in view of recent studies linking it to an increased risk for cardiac events that may be independent of other symptoms of depression (48, 49).

Limitations

The study sample size was smaller than is recommended for reliable network analyses. We were unable to fit reliable data imputation models for missing post-treatment BDI-II symptom scores due to the high ratio of auxiliary variables to the number of participants. Although none of the medical and demographic variables that were assessed for this study differed between patients with or without the most common residual symptoms at 16 weeks, not all variables were measured. Questionnaires rather than polysomnography or actigraphy were used to assess sleep quality and physical activity. Differential item reliability and difficulty may have affected the pattern of results in the network analysis (41).

Conclusions and Recommendations

The results of other depression treatment trials in patients with CHD should be used to confirm whether fatigue and loss of energy are common residual symptoms. If they are, then

additional studies will be needed to determine the significance of these symptoms for depression treatment outcomes including the risk for relapse, and the risk of cardiac events. Although these symptoms may in part reflect the underlying cardiac illness, it is important to note that fatigue and loss of energy are common before treatment and as residual symptoms following treatment in medically well depressed psychiatric patients, suggesting that they are part of the depression syndrome.

Despite the small sample size, the results of the network analyses suggest a potential model for identifying patients whose depression will likely not remit with standard depression treatment, based on the centrality of common residual symptoms such as fatigue with the remaining depression symptoms. This possibility should be explored in future studies with larger samples of depressed patients with CHD.

Finally, research is needed to determine how best to treat fatigue or loss of energy and loss of interest or pleasure either during or following standard depression treatment. There is little evidence that any type of psychotherapy or antidepressant has a greater effect than any other on a specific depression symptom (50–53). However, this has not been adequately studied in depressed cardiac patients. Vital exhaustion, a construct related to depression, includes fatigue as one of the central symptoms of the disorder (54). Appels and his colleagues, who first described vital exhaustion and its association with cardiovascular morbidity and mortality, tested a group intervention designed to reduce stress leading to fatigue and related symptoms, and to make rest more efficient in patients complaining of fatigue and exhaustion after percutaneous coronary intervention (55). The intervention reduced reports of exhaustion and fatigue in the overall sample, but not the risk for future cardiac events. Exercise training has also been shown to reduce fatigue, increase activity, and to be at least modestly effective in improving depression (56–59), including patients with CHD (60, 61). Exercise could be tried along with standard antidepressant therapy or as a stand-alone treatment. Stress management and other components of the EXIT intervention (55) could also be tried when fatigue or loss of energy remain following standard depression treatment.

To the extent that insomnia contributes to symptoms of fatigue or loss of energy, CBT for disordered sleep could be tested as an adjunctive intervention. A meta-analysis of CBT for insomnia in depressed patients showed a three-fold higher likelihood of depression remission compared to control conditions (62). Alternately, melatonin agonists may be tried as monotherapy or to augment standard antidepressants. The safety profile of these drugs has not been determined in cardiac patients, but they appear to be free of cardiovascular side effects (63).

In conclusion, fatigue and loss of energy often continue to be reported even after otherwise successful treatment for major depression, and these residual symptoms are associated both with relapse and an increased risk for mortality in patients with CHD. In this study of depressed patients with stable CHD, the persistence of these symptoms following standard depression treatment was not predicted by baseline demographic variables, medical comorbidities, anxiety, depression severity, thyroid hormone levels, or markers of

inflammation. More research is needed to clarify the clinical significance of residual depression symptoms and to develop effective interventions for them.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BDI-II	Beck Depression Inventory 2
HAM-D-17	Hamilton Depression Inventory-17 item
BAI	Beck Depression Anxiety Inventory
CBT	cognitive behavior therapy
CHD	coronary heart disease
DISH	Depression Interview and Structured Hamilton
hsCRP	High sensitivity C-reactive protein
IL-6	Interleukin-6
IPAQ	International Physical Activity Questionnaire
PSQI	Pittsburgh Sleep Quality Index
SSRI	selective serotonin reuptake inhibitor
TNF	Tumor necrosis factor

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Figure 1. Three measures of centrality in the network analysis of the ten most common symptoms of depression in this study for remitted and nonremitted patients

The x-axis presents centrality indices as z-scores. The continuous line represents the standardized centrality score for each symptom for the remitters. The broken line represents the standardized score for each symptom for the nonremitters.

Table 1

BDI-II symptoms at baseline and post treatment (N=125)

Symptom	Present/Present N (%)	Present/Absent N (%)	Absent/Present N (%)	Absent/Absent N (%)
Sadness	24 (19.1)	97 (77.0)	1 (0.8)	4 (3.2)
Pessimism	44 (34.9)	78 (61.9)	0 (0.0)	4 (3.2)
Past Failure	41 (32.5)	71 (56.4)	3 (2.4)	11 (8.7)
Loss of Pleasure	65 (51.6)	59 (46.8)	2 (1.6)	2 (1.6)
Guilty Feelings	26 (20.6)	83 (65.9)	1 (0.8)	16 (12.7)
Punishment Feelings	14 (11.1)	41 (32.5)	2 (1.6)	69 (54.8)
Self-Dislike	28 (22.2)	86 (68.3)	0 (0.0)	12 (9.5)
Self-Criticalness	43 (34.1)	71 (56.4)	1 (0.8)	11 (8.7)
Suicidal Thoughts	4 (3.2)	31 (24.6)	1 (0.8)	90 (71.4)
Crying	18 (14.3)	73 (57.9)	1 (0.8)	34 (27.0)
Agitation	33 (26.2)	69 (54.8)	6 (4.8)	18 (14.3)
Loss of Interest	57 (45.2)	64 (50.8)	1 (0.8)	4 (3.2)
Indecisiveness	33 (26.2)	78 (61.9)	0 (0.0)	15 (11.9)
Worthlessness	32 (25.4)	78 (61.9)	3 (2.4)	13 (10.3)
Loss of Energy	87 (69.1)	38 (30.2)	0 (0.0)	1 (0.8)
Insomnia	22 (17.5)	46 (36.5)	8 (6.4)	50 (39.7)
Hypersomnia	13 (10.3)	39 (31.0)	13 (10.3)	61 (48.4)
Irritability	24 (19.1)	85 (67.5)	2 (1.6)	15 (11.9)
Decreased Appetite	21 (16.7)	36 (28.6)	14 (11.1)	55 (43.7)
Increased Appetite	12 (9.5)	39 (31.0)	8 (6.4)	67 (53.2)
Concentration Difficulty	50 (39.7)	69 (54.8)	1 (0.8)	6 (4.8)
Tiredness or Fatigue	70 (55.6)	53 (42.1)	0 (0.0)	3 (2.4)
Loss of Interest in Sex	16 (12.7)	89 (70.6)	4 (3.2)	17 (13.5)

Table 2

Medical and demographic characteristics of patients with loss of energy and fatigue present at both pre and post treatment vs. at pretreatment only.

Characteristic	BDI-II Symptom					
	Loss of Energy			Tiredness or Fatigue		
	Present/Present (n=87)	Present/Absent (n=38)	P	Present/Present (n=70)	Present/Absent (n=53)	P
Demographics						
Age	60.3 ± 8.9	58.2 ± 7.9	0.22	60.4 ± 8.4	58.6 ± 8.9	0.26
Female	36 (41.4)	16 (42.1)	0.94	32 (45.7)	20 (37.7)	0.38
White	72 (82.8)	34 (89.5)	0.34	59 (84.3)	45 (84.9)	0.92
Education (12+ years)	84 (96.6)	36 (94.7)	0.64	67 (95.7)	51 (96.2)	0.99
Medical						
History of MI	56 (64.4)	23 (60.5)	0.68	41 (58.6)	36 (67.9)	0.29
CHF (Class I-II)	18 (20.7)	6 (15.8)	0.52	10 (14.3)	14 (26.4)	0.093
Diabetes	41 (47.1)	14 (36.8)	0.29	34 (48.6)	21 (39.6)	0.32
Hypertension	74 (85.1)	29 (76.3)	0.24	59 (84.3)	42 (79.3)	0.47
Revascularization	82 (94.3)	36 (94.7)	0.99	67 (95.7)	49 (92.5)	0.44
BMI (kg/m ²)	32.0 ± 6.1	31.4 ± 6.1	0.58	31.6 ± 5.7	32.3 ± 6.5	0.52
Current smoker	20 (23.0)	10 (26.3)	0.69	12 (17.1)	18 (34.0)	0.032
Medications						
Beta blockers	71 (81.6)	31 (81.6)	0.99	58 (82.9)	42 (79.3)	0.61
Statins	73 (83.9)	32 (84.2)	0.99	59 (84.3)	45 (84.9)	0.99
Anxiolytics	26 (29.9)	11 (29.0)	0.99	22 (31.4)	14 (26.4)	0.55

Characteristic	BDI-II Symptom					
	Loss of Energy			Tiredness or Fatigue		
	Present/Present (n=87)	Present/Absent (n=38)	P	Present/Present (n=70)	Present/Absent (n=53)	P
Medical events during TX						
Any hospitalization(s)	21 (24.1)	7 (18.4)	0.48	17 (24.3)	10 (18.9)	0.47
Any ED visit(s)	21 (24.1)	9 (23.7)	0.96	19 (27.1)	10 (18.9)	0.28
Depression/anxiety severity						
BDI-II total score	29.8 ± 8.8	30.6 ± 8.3	0.64	30.6 ± 9.1	29.8 ± 7.8	0.60
HAM-D total score	22.6 ± 5.9	23.8 ± 5.5	0.30	22.8 ± 6.0	23.3 ± 5.5	0.64
BAI total score	13.4 ± 8.8	15.0 ± 7.6	0.32	14.0 ± 9.2	14.0 ± 7.5	0.99
Sleep Quality						
PSQI Global Score	10.9 ± 4.0	9.6 ± 4.3	0.081	11.3 ± 4.1	9.7 ± 3.8	0.029
Physical Activity						
IPAQ usual activity rating			0.44			0.94
Low	37 (42.5)	12 (31.6)		27 (38.6)	22 (41.5)	
Moderate	32 (36.8)	15 (39.5)		27 (38.6)	20 (37.7)	
High	18 (20.7)	11 (29.0)		16 (22.9)	11 (20.8)	
Inflammatory Markers						
CRP mg/dl	0.43 ± 0.49	0.31 ± 0.29	0.20	0.37 ± 0.46	0.43 ± 0.45	0.47
IL-6 pg/ml	2.01 ± 1.92	1.53 ± 1.02	0.16	1.74 ± 1.42	2.02 ± 2.03	0.39
TNF pg/ml	2.04 ± 1.36	1.78 ± 0.46	0.28	2.04 ± 1.50	1.86 ± 0.48	0.43
Thyroid Hormone Levels						

Characteristic	BDI-II Symptom					
	Loss of Energy			Tiredness or Fatigue		
	Present/Present (n=87)	Present/Absent (n=38)	P	Present/Present (n=70)	Present/Absent (n=53)	P
Free T4	2.34 ± 0.57	2.25 ± 0.45	0.36	2.38 ± 0.58	2.21 ± 0.44	0.070
T4 Total (mcg/dl)	7.63 ± 1.77	7.49 ± 1.69	0.68	7.80 ± 1.89	7.29 ± 1.42	0.11
Nighttime Heart Rate						
Nighttime HR (bpm)	67.8 ± 10.7	67.8 ± 12.3	0.99	67.0 ± 9.9	69.5 ± 12.1	0.23