Published in final edited form as:

Int J Psychiatry Med. 2018 July ; 53(4): 256–272. doi:10.1177/0091217417749796.

Multimethod assessment of baseline depression and relationship to hepatitis C treatment discontinuation

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Abstract

Objective—The primary study objective is to determine which measures of depression are associated with early discontinuation of hepatitis C virus infection treatment and to determine which measure best characterizes the depression that develops during treatment.

Methods—Seventy-eight treatment-naïve subjects who initiated pegylated interfer-on/ribavirin treatment for hepatitis C virus infection were included. Baseline depression was assessed with the Structured Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), the Hamilton Depression Rating Scale, and the Beck Depression Inventory-II. The latter two measures were repeated at treatment weeks 12 and 24.

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Authors' contribution

JJW—Conception and design of the study, acquisition and analysis of data, drafting the manuscript or figures; SP—Drafting the manuscript or figures; NB—Conception and design of the study; DTD—Acquisition and analysis of data; SMM—Acquisition and analysis of data; AS—Acquisition and analysis of data; JMG—Conception and design of the study, drafting the manuscript or figures.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Weiss reports grants from NIH during the conduct of the study, personal fees from Gilead, and personal fees from AbbVie. Dr Dieterich consults for and receives honoraria from Gilead, AbbVie, and BMS. Dr Gorman owns Franklin Behavioral Health Consultants and Critica LLC. He receives consulting fees from Care Management Technologies, Inc. and royalties from Oxford University Press. He is on the board of directors for UJA-Federation of NY and the Hebrew Institute of Riverdale. He owns stocks in Arbutus, Amphastar, BWX Technologies, Genocoe Biosciences, Orexigen, Rite Aid, Trevena, Cytokinetics, Epizyme, Kite, Neurologix, Orexigen, Oramed, Pacific Biosciences, Protalix, RXI, Sangamo, Synergy, and Xencor. The remaining authors declare no conflict of interest.

Results—Depression scores, as measured by the three instruments, lacked adequate consistency. Baseline depression as measured by the Beck Depression Inventory-II, but not by the other scales, was associated with early treatment discontinuation at weeks 12 and 24. Changes in depression during treatment were restricted to somatic symptoms. Of those who completed treatment, those who were *not* depressed at baseline tended to demonstrate significant depression increases during treatment.

Conclusion—The Beck Depression Inventory-II is recommended to assess depression prior to hepatitis C virus infection treatment. Somatic symptoms of depression should be monitored during treatment. Baseline depression as measured by the Beck Depression Inventory-II was associated with early treatment discontinuation. The Beck Depression Inventory-II, Structured Interview for DSM-IV, and Hamilton Depression Rating Scale yielded results that were not consistent with each other in this sample. Future research should focus on standardizing depression assessment in medically ill populations to identify measures that predict treatment discontinuation.

Keywords

assessment; depression; interferon; hepatitis C; HIV

Introduction

Research has focused on the best method of assessing depression in medically ill populations because of a potential overlap between somatic symptoms used to diagnose depression and those caused by the medical illness.^{1–7} Research that has investigated this overlap is inconclusive thus far due to conflicting findings. Some prior research has shown that medical illnesses might influence assessment of depression, while other studies have shown that somatic symptoms are not less valid indicators of depression among medically ill populations. Thombs et al.,¹ for example, found that somatic symptoms did not inflate scores of depression among patients following an acute myocardial infarction when compared to psychiatry outpatients who were matched on various characteristics, and another study reported that patterns of somatic symptoms were similar among patients with or without chronic illness.⁵ On the other hand, some research has found that conditions such as migraines or systemic sclerosis may cause an increase in depression scores due to somatic symptoms related to the medical illness,^{6,8,9} and other research has shown that severity of medical illness is correlated to somatic items on the Beck Depression Inventory-II (BDI-II).⁷ Having an accurate understanding of the impact that somatic symptoms play on the diagnosis of depression can inform physicians and researchers as to the best approaches to treat these patients.

Adults with hepatitis C virus (HCV) infection treated with pegylated interferon-alfa (IFN) and ribavirin (RBV) are at an increased risk for incident depression during treatment^{10–16} and the presence of baseline depression enhances that risk.^{14,17,18} These observations led to disqualification of some patients with depression histories from receiving HCV therapy.^{19–23} In other cases, clinicians opted to first treat baseline depression prior to initiating treatment for hepatitis C or to place hepatitis C-infected patients with no baseline depression but a history of depression on prophylactic antidepressant therapy. Evidence supporting the use of prophylactic antidepressant therapy in the absence of baseline depression is mixed with

some studies finding support for this practice^{24–27} and others finding no support for it.^{28–31} Although IFN is no longer used to treat HCV, IFN remains today a treatment option for multiple sclerosis and various cancers including leukemia and melanoma.^{32–34} RBV continues to be used to treat HCV in some patients. Additionally, IFN and RBV may be used in combination for the treatment of special cases of human papillomavirus infection.^{35–37} Thus, the findings of this study may have clinical implications for other areas of medical care.

Studies are mixed as to whether the presence of depression at the time of HCV treatment initiation or during treatment actually affects HCV treatment outcomes. Some studies have shown that patients meeting criteria for a major depressive episode or who have elevated depression symptom rating scores at baseline are less likely to adhere to IFN/RBV therapy^{22–26} and/or to have lower rates of sustained virologic response (SVR).^{11,38} The majority of studies, however, have found no effect of depression or depression symptoms at baseline on early treatment discontinuation or SVR.^{39–47} One study found that baseline depression did lead to more treatment discontinuation but did not impact SVR rates.⁴⁸ Another study that excluded subjects with a history of depression found that the development of depression during treatment positively predicted achievement of SVR.⁴⁹

This variability in findings concerning the relationship between baseline depression and antiviral discontinuation may be due in part to widely differing criteria for depression. Some studies defined depression as a syndrome, using structured interviews and established criteria such as DSM-IV. Others used cutoffs on rating scales like the BDI-II and the Hamilton Depression Rating Scale (HAM-D) and vary as to what cutoffs are used. There is variability in the way that depression scales are meant to be administered, as well as the number of questions targeting somatic symptoms. Although the BDI-II, HAM-D, and Structured Clinical Interview for DSM-IV (SCID) evaluate different aspects of a patient's depression, it is essential to know which instruments predict clinical outcomes such as treatment discontinuation with higher accuracy. The purpose of this study is to compare the three different instruments measuring depression in order to understand their relationships with treatment discontinuation and the ways in which somatic symptoms influence the diagnosis of depression in 78 patients who began IFN/RBV therapy.

Methods

Study design

One hundred and two patients with confirmed chronic HCV infection who had decided with their physicians to begin a course of IFN/RBV therapy within the following two months were recruited for this study. Patients were treated within multidisciplinary, specialty clinics for HCV-infected patients at an academic medical center and Veteran's Administration Medical Center in New York City.^{50,51} Of the four recruitment sites, only one exclusively treated patients with HIV. Participants were at least 18 years old, spoke English or Spanish, had never received IFN/RBV, and had never received a liver transplant. Informed consent was obtained after explaining study procedures to the participants. Twenty-four of the 102 participants did not begin treatment for HCV, while the other 78 began IFN/RBV therapy and were followed longitudinally. Thirty-two of these 78 patients were coinfecting with HIV.

Assessment instruments

Each patient underwent a SCID supervised by a psychologist at baseline, before receiving IFN/RBV. Lifetime and current psychiatric diagnosis were recorded. Due to the length of time required for administration, the SCID was not repeated. Patients were also administered a 17-item HAM-D⁵² and 21-item BDI rating scales at baseline, as well as at weeks 12 and 24 of treatment. One participant completed the SCID but was unable to complete the HAM-D and BDI rating scales during their baseline interview. Measures of HCV viral load and reasons for treatment discontinuation were abstracted from each patient's medical record at baseline and throughout treatment.

Current depression was assessed in three ways: (1) On the basis of DSM-IV-TR criteria for major depressive disorder (MDD) using the SCID, (2) a cutoff on the HAM-D of >7 , and (3) a cutoff on the BDI-II of >13 .⁵³ Additionally, BDI-II items were divided into somatic and cognitive-affective symptoms based on a factor analysis of the BDI-II in patients with chronic HCV.⁵⁴ Although there are different ways to categorize BDI-II items, the current study modeled their methods after a previous study looking at patients with HCV.⁵⁴ Somatic symptoms included the following: loss of energy, change in sleep patterns, irritability, change in appetite, concentration difficulties, tiredness and/or fatigue, and loss of interest in sex. Cognitive-affective symptoms included the following: sadness, pessimism, past failures, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal thoughts or wishes, crying, agitation, and worthlessness. Three BDI-II items were eliminated in this factor analysis (loss of pleasure, loss of interest, and indecisiveness).

Statistical analyses

The number of patients who discontinued IFN/RBV treatment at 12 and 24 weeks was compared between the groups with and without depression at baseline using mixed effects logistic regression. A separate regression analysis was done for each of the three measures of depression and for the composite of whether or not subjects were depressed on any of the three depression measures at baseline. In addition, the subgroup of patients who discontinued therapy was further subdivided into those who did so because of lack of virologic response and those who discontinued because of adverse side effects. The above regression analyses were repeated after excluding those who discontinued due to lack of virologic response. Chi-square analyses were used to compare the proportion of patients who achieved SVR between the groups with and without depression at baseline.

Somatic and cognitive domains of the BDI-II were compared at the three time periods (baseline, 12 weeks, and 24 weeks) for the entire group of patients and for the BDI-II defined depressed and nondepressed groups at baseline separately to determine if one of these two domains worsened more than the other. Each of the 21 BDI-II items was compared separately at the three time points using mixed effects regression to determine which symptoms worsened the most during IFN/RBV treatment.

Statistical analyses were conducted using SPSS version 19 and SuperMix. All significance levels are two tailed and level of significance was set at $p < 0.05$.

The study was approved by the Icahn School of Medicine at Mount Sinai and Bronx Veteran's Administration Medical Center Institutional Review Boards and written informed consent was obtained from all subjects.

Results

Sample characteristics

When baseline depression was defined according to BDI-II criteria, there were no differences between the depressed and nondepressed groups in mean age, sex, education, ethnicity, HCV viral load, HCV genotype, METAVIR Fibrosis Liver Stage, HIV coinfection, history of intravenous drug use, or antidepressant use at baseline (see Table 1). Participants who had depression at baseline were more likely to have a previous history of the following: psychiatric hospitalization, suicide attempts, incarceration, and a diagnosis of substance use disorder and psychiatric diagnosis.

Two of the eight patients with SCID-diagnosed MDD were not on antidepressants at baseline and both of them began them in the first 12 weeks of treatment. Fifty-one of the 70 subjects without MDD were not on antidepressants at baseline. Of these 51 participants, seven began antidepressant medication during the first 24 weeks of treatment.

Consistency of assessment of depression at baseline across three measures

The HAM-D criterion was most likely to diagnose depression (37.7% of cases), followed by BDI-II (26.9%) and SCID (10.3%). When depression is defined as meeting criteria on any of the three measures, then 47.4% of the sample was depressed at baseline. Table 2 shows the relationships among baseline depression based on SCID, BDI-II, and HAM-D criteria. Despite the fact that the SCID diagnosed the fewest number of cases of depression, only five of the eight patients with MDD diagnosed by SCID criteria met BDI or HAM-D criteria, respectively. A diagnosis of depression based on BDI-II criteria was corroborated on the HAM-D in 71.4% of cases but a diagnosis of depression based on HAM-D criteria was corroborated on the BDI-II in only 51.7% of cases. Thus, the specific subjects diagnosed as depressed by these three measures in this population of patients with chronic hepatitis C infection differ considerably across them.

Depression as a predictor of treatment discontinuation and SVR

Overall, 52 of the 78 patients (67%) completed 24 weeks of IFN/RBV therapy and 23 out of the 78 (29%) eventually had a SVR, regarded as a cure. Table 3 shows that there were no differences in discontinuation from IFN/RBV treatment between the depressed and nondepressed groups when the SCID and HAM-D were used to define baseline depression or if all three criteria were used together. SCID identification of depression was associated with higher rates of treatment discontinuation; while not statistically significant this may be due to inadequate power due to small sample size. There were statistically higher rates of early treatment discontinuation in the depressed group as defined by the BDI-II at baseline at both 12 and 24 weeks of treatment. These results did not change when those who were discontinued by the medical provider due to lack of virologic response ($n=5$) were excluded from the analyses. Table 3 also shows the same lack of difference for SVR between the

groups regardless of how baseline depression was defined. There was no significant difference in SVR rates between individuals who were coinfecting with HCV and HIV as compared to individuals who only had HCV.

Influence of somatic symptoms on changes in depression

In the group of HCV patients as a whole, mean BDI-II total item score increased from 0.46 (SD= 0.48) at baseline to 0.63 (SD= 0.46) at 12 weeks and 0.52 (SD= 0.52) at 24 weeks. The 12- and 24-week total item scores were not significantly higher when compared to baseline. When broken down into mean somatic item scores and mean cognitive–affective item scores, significant increases were found from baseline to 12 and 24 weeks on the somatic scale but not on the cognitive–affective scale (Table 4). When these results were analyzed separately for those who were not depressed at baseline on BDI-II criteria and those who were, the results were informative. For those who were depressed at baseline on BDI-II criteria, there were no significant increases with HCV treatment on total, somatic, or cognitive–affective BDI item means. However, for those who were not depressed at baseline on BDI-II criteria, there were significant increases on HCV treatment on total, somatic, and cognitive–affective BDI-II item means. When only those who completed 24 weeks of treatment were analyzed, there were significant increases in total BDI-II score and BDI-II somatic in the entire group and in the group who were not depressed at baseline. BDI-II cognitive–affective item means did not exhibit a significant increase.

Table 5 shows changes in the 21 individual items of the BDI-II scale from baseline to 12 and 24 weeks for all subjects and for those subjects who remained on treatment at week 24. The five items with significant increases from baseline in those who remained on treatment through week 24 were all on the somatic dimension: loss of energy ($p = 0.01$), irritability ($p = 0.01$), tiredness or fatigue ($p = 0.00$), loss of interest in sex ($p = 0.04$), and changes in appetite ($p = 0.05$). Although not quite statistically significant, there was a trend for concentration difficulty to also increase from baseline ($p = 0.06$).

Discussion

The purpose of this study was to compare three validated measures of depression in their ability to determine which measures of depression are associated with early discontinuation of hepatitis C treatment. Consistent with previous research,⁵⁵ results indicated that the instrument used to measure depression had an effect on the number of people who met depression criteria (ranging from 10.3 to 37.7%). Specifically, very low agreement was found between SCID diagnoses and both rating scales. Agreement between the HAM-D and BDI-II was also low in this sample. Several studies have questioned the validity of rating scales for depression that include somatic symptoms in the evaluation of patients with hepatitis C.^{54,56}

There may be several reasons for the observed discrepancies between these widely used depression measures. While a structured psychiatric interview, such as the SCID, provides the opportunity to differentiate between symptoms related to medical illness and those attributable to depression, this is not possible with self-report such as the BDI-II. The HAM-D is clinician administered, but symptoms contribute to patient's scores regardless of

etiology. Discrepancies among these depression measures may account for conflicting findings in previous research on this topic. In agreement with previous research, we recommend using the BDI-II for assessment of depression comorbid to illnesses with somatic symptoms.^{16,55}

The data reported here suggest that baseline depression status does not influence SVR, and therefore should not influence the decision to offer treatment to patients with HCV infection. However, this recommendation is dependent upon the tool used to assess depression. Treatment discontinuation was not affected by baseline depression when measured by the SCID or HAM-D. On the other hand, using relatively liberal BDI-II criteria (<13) for depression, we did observe an effect of baseline depression on the rate of HCV treatment discontinuation. For those who remained on treatment through week 24, however, it was particularly those who were not depressed at baseline that showed significant increases in depression.

There are several potential limitations of the current study. Forty-one percent of this sample was coinfectd with HIV, while it is estimated that about 5–10% of HCV patients are coinfectd with HIV in the United States of America. This discrepancy severely decreases external validity of this study. This is particularly important given that previous research has found that coinfectd patients have unique characteristics that may make them less vulnerable to developing depressive symptoms during IFN treatment.⁵⁷ It is also important to consider the context in which the patient sample is treated. Participants in this study were recruited from an academic medical center, where they had access to numerous specialists and mental health resources. It is possible that patients in a different setting may experience a greater effect of baseline depression on their treatment discontinuation rates. Another potential limitation is that the patient sample was treated with an array of antidepressant medications. These treatment differences were not included in the analysis.

A potential direction for future research is to focus on whether somatic symptoms influence patients with HCV differently depending on whether they are coinfectd with HIV. Additionally, participants in this study were treated with PEG-IFN/RBV. Future research should focus on the influence of depression on SVR with newer direct acting antiviral medications. Most importantly, ongoing research is required to investigate the differences between the depression measures discussed in this paper. These validated and widely employed measures should not be used interchangeably to assess depression in medical populations, as it appears that they are in fact capturing distinct aspects of depression.

Acknowledgments

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Mental Health or the National Institutes of Health.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by the National Institute of Mental Health of the National Institutes of Health, grant number MH071177.

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Table 1

Baseline characteristics: Differences between depressed and nondepressed subjects.

	BDI >13 (n =21)	BDI 13 (n =56)		
	M (SD) or %	M (SD) or %	t(df) or χ^2	p
Age (years)	52.5 (7.8)	51.3 (12.7)	t(76) = -0.40	0.69
Sex (male)	81.0	73.2		0.57
Education (years)	12.2 (2.5)	13.0 (3.0)	t(76) = 1.07	0.29
Ethnicity			$\chi^2 = 0.96$	0.62
Black	28.6	35.7		
Hispanic	38.1	26.8		
White	33.3	37.5		
HCV RNA (log ₁₀ IU/ml)	6.1 (1.2)	6.3 (0.7)	t(76) = 0.81	0.48
HCV genotype (type 1)	85.7	71.4		0.25
Liver stage			$\chi^2 = 2.58$	0.28
No staging	4.8	17.9		
Stage 1 or 2	33.3	35.7		
Stage 3 or 4	61.9	46.4		
HIV coinfection	23.8	48.2		0.07
History of SUD diagnosis	95.2	67.9		0.016
History of psychiatric diagnosis	95.2	57.1		0.001
Past psychiatric hospitalization	42.9	14.3		0.012
Past suicide attempt	38.1	8.9		0.005
History of incarceration	76.2	44.6		0.02
History of IVDU	61.9	46.4		0.31
On antidepressant at study baseline	47.6	26.8		0.10

BDI: Beck Depression Inventory; HCV: hepatitis C virus; IVDU: Intravenous Drug Use; SD: standard deviation; SUD: Substance Use Disorder Diagnosis.

Bold indicates significant findings at p<.05.

Table 2

Relationship among the three depression measures at baseline (BDI-II, HAM-D, SCID).

Comparator:	BDI-II + (n =21)	HAM-D + (n =29)	SCID+ (n =8)
Measure			
SCID+ (n=8) ^a	62.5% (n=5)	62.5% (n=5)	
SCID- (n=70)	22.9% (n=16)	34.3% (n=24)	
HAM-D+ (n=29) ^c	51.7% (n=15)		17.2% (n=5)
HAM-D- (n=48)	12.5% (n=6)		6.3% (n=3)
BDI-II+ (n=21) ^b		71.4% (n=15)	23.8% (n=5)
BDI-II- (n=56)		25.0% (n=14)	5.4% (n=3)

BDI-II: Beck Depression Inventory-II; HAM-D: Hamilton Depression Rating Scale; SCID: Structured Clinical Interview for DSM-IV.

^aSCID +=Diagnosis of current MDD.

^bBDI-II +=Score of greater than 13.

^cHAM-D +=Score of greater than 7.

Table 3

Twelve- and 24-week treatment rates and sustained virologic response (SVR) rates between baseline depression groups.

	Percent on treatment, week 12		Percent on treatment, week 24		Percent SVR	
		p		p		p
All subjects (N=78)						
SCID+ (n=8)	75.0	0.91	50.0	0.90	37.5	0.69
SCID- (n=70)	84.3		68.6		28.6	
BDI-II+ (n=21)	66.7	0.003	42.9	0.018	33.3	0.58
BDI-II- (n=56)	89.3		75.0		26.8	
HAM-D+ (n=29)	86.2	0.82	65.5	0.81	34.5	0.44
HAM-D- (n=48)	81.3		66.7		25.0	
Any of three + (n=37)	81.1	0.67	59.5	0.37	32.4	0.61
All three- (n=40)	85.0		72.5		25.0	
Excluding subjects who discontinued due to lack of virologic response (N=73)						
SCID+ (n=8)			50.0	0.91	37.5	0.70
SCID- (n=65)			73.8		30.8	
BDI-II+ (n=20)			45.0	<0.001	35.0	0.78
BDI-II- (n=52)			80.8		28.8	
HAM-D+ (n=27)			70.4	0.73	37.0	0.43
HAM-D- (n=45)			71.1		26.7	
Any of three+ (n=35)			62.9	0.36	34.3	0.61
All three- (n=37)			78.4		27.0	

BDI-II: Beck Depression Inventory-II; HAM-D: Hamilton Depression Rating Scale; SCID: Structured Clinical Interview for DSM-IV.

Bold indicates significant findings at $p < .05$.

Table 4

Change over time in average total, somatic, and cognitive–affective BDI-II scores for groups by baseline depression and treatment completion.

	Mean BDI total avg. (SD)	Mean BDI somatic avg. (SD)	Mean BDI cog-aff avg. (SD)
Entire sample			
Baseline (n=77)	0.46 (0.48)	0.59 (0.53)	0.37 (0.48)
12 week (n=71)	0.63 (0.46)	0.89 (0.51)	0.47 (0.51)
24 week (n=66)	0.52 (0.47)	0.75 (0.56)	0.46 (0.38)
Time Effect (p value)	0.13	0.01	0.53
Nondepressed on BDI at baseline			
Baseline (n=56)	0.22 (0.19)	0.36 (0.31)	0.13 (0.16)
12 weeks (n=53)	0.49 (0.38)	0.79 (0.47)	0.30 (0.40)
24 weeks (n=51)	0.38 (0.35)	0.63 (0.51)	0.24 (0.34)
Time Effect (p value)	0.00	0.00	0.03
Depressed on BDI at baseline			
Baseline (n=21)	1.1 (0.44)	1.2 (0.52)	1.0 (0.45)
12 weeks (n=18)	1.0 (0.44)	1.2 (0.51)	0.96 (0.50)
24 weeks (n=15)	1.0 (0.51)	1.2 (0.54)	1.0 (0.51)
Time Effect (p value)	0.36	0.85	0.14
Completed 24 weeks of HCV treatment			
24-week completers—BDI at baseline (n=51)	0.40 (0.43)	0.51 (0.45)	0.32 (0.44)
24-week completers—BDI at 12 weeks (n=49)	0.57 (0.42)	0.86 (0.50)	0.38 (0.43)
24-week completers—BDI at 24 weeks (n=45)	0.50 (0.43)	0.79 (0.55)	0.33 (0.38)
Time effect (p value)	0.03	0.00	0.70
Completed 24 weeks of HCV treatment and were not depressed on BDI at baseline			
BDI at baseline (n=42)	0.24 (0.21)	0.39 (0.32)	0.14 (0.17)
BDI at 12 weeks (n=41)	0.45 (0.31)	0.78 (0.44)	0.24 (0.29)
BDI at 24 weeks (n=38)	0.36 (0.25)	0.67 (0.46)	0.19 (0.20)
Time effect (p value)	0.01	0.00	0.28
Completed 24 weeks of HCV treatment and were depressed on BDI at baseline			
BDI at baseline (n=9)	1.11 (0.48)	1.05 (0.57)	1.12 (0.44)
BDI at 12 weeks (n=8)	1.19 (0.37)	1.30 (0.59)	1.07 (0.36)
BDI at 24 weeks (n=7)	1.29 (0.38)	1.41 (0.62)	1.08 (0.24)
Time effect (p value)	0.38	0.18	0.89

BDI: Beck Depression Inventory; HCV: hepatitis C virus; SD: standard deviation.

Bold indicates significant findings at $p < .05$.

BDI-II individual item changes over time in entire sample and 24-week treatment completers—means (SD).

Table 5

BDI item	All—BL (n =77)	All—12 weeks (n =71)	All—24 weeks (n =66)	Time effect (p value) ^a	Completers—BL (n =51)	Completers—12 (n =49)	Completers—24 (n =45)	Time effect (p value) ^a
Sadness	0.32 (0.62)	0.51 (0.77)	0.36 (0.57)	0.60	0.29 (0.54)	0.49 (0.77)	0.31 (0.47)	0.65
CA								
Pessimism	0.36 (0.65)	0.55 (0.82)	0.44 (0.77)	0.31	0.37 (0.69)	0.41 (0.71)	0.33 (0.67)	0.69
CA								
Past failure	0.58 (0.80)	0.70 (0.89)	0.58 (0.73)	0.76	0.55 (0.78)	0.57 (0.79)	0.44 (0.66)	0.41
CA								
Loss of pleasure	0.57 (0.66)	0.72 (0.80)	0.59 (0.76)	0.65	0.49 (0.64)	0.67 (0.80)	0.62 (0.81)	0.14
E								
Guilty feelings	0.48 (0.68)	0.46 (0.65)	0.39 (0.52)	0.31	0.47 (0.70)	0.41 (0.67)	0.36 (0.48)	0.20
CA								
Punishment feelings	0.34 (0.84)	0.45 (0.92)	0.26 (0.64)	0.49	0.20 (0.60)	0.29 (0.74)	0.18 (0.44)	0.79
CA								
Self-dislike	0.48 (0.85)	0.62 (0.83)	0.36 (0.72)	0.39	0.39 (0.78)	0.45 (0.74)	0.36 (0.71)	0.80
CA								
Self-criticalness	0.42 (0.82)	0.48 (0.75)	0.39 (0.68)	0.94	0.29 (0.64)	0.39 (0.67)	0.38 (0.65)	0.53
CA								
Suicidal thoughts	0.06 (0.25)	0.13 (0.34)	0.11 (0.31)	0.23	0.06 (0.24)	0.08 (0.28)	0.09 (0.29)	0.33
CA								
Crying	0.38 (0.84)	0.46 (0.88)	0.50 (0.93)	0.17	0.27 (0.67)	0.37 (0.70)	0.40 (0.69)	0.20
CA								
Agitation	0.40 (0.71)	0.46 (0.67)	0.48 (0.71)	0.27	0.33 (0.52)	0.47 (0.65)	0.47 (0.66)	0.14
CA								
Loss of interest	0.53 (0.90)	0.80 (0.92)	0.45 (0.81)	0.65	0.47 (0.70)	0.69 (0.80)	0.51 (0.90)	0.70
E								
Indecisiveness	0.34 (0.64)	0.42 (0.73)	0.38 (0.72)	0.70	0.33 (0.62)	0.37 (0.67)	0.36 (0.68)	0.89
E								
Worthlessness	0.23 (0.61)	0.34 (0.65)	0.30 (0.68)	0.49	0.24 (0.65)	0.24 (0.52)	0.27 (0.62)	0.89
CA								

BDI item	All—BL (n =77)	All—12 weeks (n =71)	All—24 weeks (n =66)	Time effect (p value) ^a	Completers—BL (n =51)	Completers—12 (n =49)	Completers—24 (n =45)	Time effect (p value) ^a
Loss of energy	0.71 (0.67)	0.99 (0.73)	0.77 (0.70)	0.38	0.65 (0.59)	0.98 (0.78)	0.91 (0.67)	0.01
S								
Changes in sleep	0.83 (0.99)	1.2 (0.98)	1.1 (1.1)	0.04	0.78 (0.99)	1.10 (0.96)	1.07 (0.96)	0.12
S								
Irritability	0.38 (0.65)	0.66 (0.72)	0.52 (0.69)	0.16	0.31 (0.58)	0.78 (0.72)	0.62 (0.75)	0.01
S								
Changes in appetite	0.40 (0.71)	0.79 (0.77)	0.61 (0.76)	0.03	0.35 (0.69)	0.69 (0.71)	0.58 (0.69)	0.05
S								
Concentration difficulty	0.57 (0.77)	0.73 (0.76)	0.65 (0.77)	0.38	0.45 (0.67)	0.71 (0.74)	0.67 (0.77)	0.06
S								
Tiredness or fatigue	0.65 (0.74)	1.0 (0.79)	0.86 (0.89)	0.03	0.57 (0.64)	1.00 (0.74)	0.96 (0.88)	0.00
S								
Loss of interest in sex	0.61 (0.85)	0.87 (1.0)	0.74 (0.92)	0.21	0.43 (0.67)	0.78 (0.96)	0.71 (0.84)	0.04
S								

BDI-II: Beck Depression Inventory-II; BL: baseline; CA: cognitive-affective; E: excluded in factor analysis; S: somatic; SD: standard deviation.

^a Z-statistic from mixed effects regression.

Bold indicates significant findings at p<0.05.