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Vulnerability to somatic symptoms of depression during interferon-alpha therapy for hepatitis C: A 16-week prospective study

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Abstract

Objective—This study evaluated the distinctive clinical and biological manifestations of depressive symptom subtypes (i.e., cognitive–affective and somatic) in Veterans with hepatitis C viral infection (HCV) before and during interferon-alpha (IFN) based antiviral therapy.

Methods—Thirty-two Veterans with HCV and no prior history of IFN therapy were followed prospectively during the first 16 weeks of therapy to evaluate depressive symptoms and to determine if baseline cytokine and serotonin levels predicted subsequent changes in depressive scores.

Results—IFN therapy resulted in a significant increase in total depressive symptoms from baseline (week 0) to week 16, with neurovegetative and somatic symptoms of depression including loss of appetite, fatigue and irritability increasing within the first two weeks of therapy and continuing to increase throughout IFN therapy. When depressive symptoms were evaluated using a two-factor (i.e., Cognitive–Affective and Somatic) model, the Cognitive–Affective factor score did not change significantly following IFN therapy initiation, while the Somatic factor score showed a significant increase from week 0 to week 16. Veterans with the largest increases in somatic symptoms from week 0 to week 2 had significantly higher levels of tumor necrosis factor-

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Conflict of interest statement

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

Appendix A. Supplementary data

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alpha (TNF- α) and lower levels of serotonin at baseline, as compared to Veterans with minimal or no increase in somatic symptoms.

Conclusion—Somatic symptoms of depression can be significantly exacerbated during IFN therapy and may be predicted by higher TNF- α levels and lower serotonin levels at baseline.

Keywords

Cytokines; Depression; Fatigue; Hepatitis C; Interferon-alpha; Pain; Serotonin

Introduction

Approximately 2.2% of adults world-wide are chronically infected with the hepatitis C virus (HCV) [1], and approximately 10–15% of these cases progress to advanced liver disease resulting in decompensated liver cirrhosis, hepatocellular carcinoma, liver transplantation, or death [2]. Although the majority of adults with HCV avoid serious complications and live a full life span, a growing body of literature demonstrates that, even in the absence of pegylated interferon-alpha (IFN) treatment (i.e., standard antiviral therapy for HCV), many of these individuals suffer from a range of chronic neuropsychiatric impairments such as pain, fatigue, depression, and cognitive impairment. Depressive symptoms are important contributors to functional disability and decreased health-related quality of life in patients with HCV [3–5] and can further complicate the course of antiviral therapy for HCV—a treatment regimen associated with a number of neuropsychiatric toxicities, in particular, depression.

Pegylated IFN based therapies for HCV cause depression in 20–40% of patients [6–8]. The symptoms of IFN-induced depression are similar to those seen in major depressive disorder, and may include: depressed mood, irritability, emotional lability, agitation, fatigue, apathy, anhedonia, loss of appetite, psychomotor retardation, sleep disturbance, sexual dysfunction, memory impairment, and diminished ability to concentrate [9]. Suicidal ideation, suicide attempts, and completed suicides can occur during IFN based therapy but are rare. IFN-induced depressive symptoms are dose limiting, can compromise otherwise effective therapy, and are a source of considerable distress to some patients [6]. Moderate to severe depressive symptoms are a common reason for postponing or excluding patients from antiviral therapy [10], and some have reported that premorbid depression may inhibit HCV treatment effectiveness [11,12].

There are no established clinical, genetic, or physiologic risk factors that predict the development of depression during IFN-based therapies. However, it is generally believed that the frequency of serious neuropsychiatric side effects increases when IFN is given for a longer duration or at higher doses. A greater likelihood for developing depression also exists when patients with clinically significant premorbid depression (or increased depressive symptoms) are treated with IFN-based therapies [7,8,13]. We recently reported the discovery of a single nucleotide polymorphism near the interleukin 28B (interferon, lambda 3) gene (*IL28B*) that is correlated with changes in fatigue, appetite, and sleep during IFN-based therapy [14]; however, more research is needed to confirm the predictive validity and

reliability of these and other potential risk factors associated IFN-induced neuropsychiatric side effects.

Pro-inflammatory cytokines such as IFN are hypothesized to contribute to the development of depression, in part, by their effects on serotonin metabolism. IFN stimulates indolamine 2,3-dioxygenase (IDO) which leads to a peripheral depletion of tryptophan [15]. Patients on IFN therapy have altered serum levels of tryptophan (a serotonin precursor) and serotonin [16,17], and *some* of these changes in the serotonergic system are associated with increased depressive symptoms [18,19], as well as with alterations in specific cytokine levels [20]. However, more recent reports including our own findings do not support consistent correlations between IFN-induced depression and serotonin or tryptophan levels [16,21–24]. Given that both pro-inflammatory cytokines (e.g., interferons) and HCV are associated with an upregulation of indolamine 2,3 dioxygenase (an enzyme which converts tryptophan into kynurenine) [25], further research is needed to determine more sensitive markers of serotonin metabolism which could be used to predict or influence IFN-induced depression in patients with HCV.

Preclinical studies show that immunologically induced fatigue is associated with enhanced expression of brain IFN and serotonin transporter [26], and IFN administration to rats significantly reduces serotonin in the frontal cortex as well as serotonin and 5-hydroxyindoleacetic acid (a serotonin metabolite) in the midbrain and striatum [27]. Similarly, a study of 42 participants with (n=20) and without (n=22) major depressive disorder found that mRNA expression levels of the serotonin transporter, as well as interleukin-1beta (IL-1 β), IL-6, IFN- γ and tumor necrosis factor-alpha (TNF- α) are higher in those with major depressive disorder as compared with healthy controls [28]. Further, elevated pro-inflammatory cytokine mRNA levels, including TNF- α , following the start of IFN therapy are associated with the development of significant symptoms of depression [29], and patients who develop major depressive disorder during therapy have increased expression of serum IL-6 and related cytokines at baseline, as compared with patients who do not develop major depressive disorder [30]. It was recently reported that studies like these “highlight the need to develop a biomarker panel for depression that aims to profile diverse peripheral factors that together provide a biological signature of MDD (major depressive disorder) subtypes...” [31].

Although depressed mood is one of the ‘core’ symptoms of major depressive disorder, this symptom may not be as prominent in patients with HCV [32]. Other symptoms like somatic complaints, loss of appetite, fatigue, and cognitive impairments may be more prevalent. We recently completed a factor analysis of depressive symptoms [assessed with the Beck Depression Inventory, Second Edition (BDI-II)] in 671 Veterans with HCV and identified two factors Cognitive–Affective and Somatic [32]. The Cognitive–Affective factor consists of 11 BDI-II items (i.e., sadness, pessimism, past failure, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal thoughts, crying, agitation, worthlessness) and the Somatic factor consists of 7 items (i.e., loss of energy, changes in sleeping pattern, irritability, changes in appetite, concentration difficulty, tiredness or fatigue, loss of interest in sex). In patients with HCV, these symptoms may also be more problematic during IFN

therapy and resistant to antidepressant medications, as is observed in geriatric depression [33,34], or in depression due to a general medical condition [33].

The purpose of the present study, therefore, was to evaluate prospectively the development of specific depressive symptom in HCV patients during IFN therapy to determine their distinctive clinical and biological manifestations. Individuals with HCV were followed prospectively during the first 16 weeks of antiviral therapy to monitor depressive symptoms (cognitive–affective and somatic symptoms), measure cytokine and serotonin levels, and determine if baseline cytokine and serotonin levels predicted subsequent changes in depressive scores.

Methods

Participants

Thirty-two research Veterans were recruited from the Portland VA Medical Center and VA Long Beach Health Care System prior to initiating antiviral therapy. The research participants described herein are a subset of patients reported on previously [14]. In brief, participants were potentially eligible if there were at least 18 years old and initiating IFN therapy at one of the two sites. Exclusion criteria included: diagnosis of active: major depressive disorder, psychotic symptoms, or bipolar disorder (or history of bipolar disorder) during the previous 3 months [according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria, as determined by the Structured Clinical Interview for DSM-IV (SCID)], current use of antidepressant medications for any reason, or currently abusing any substances such as alcohol or intravenous drugs, or having abused in the past 3 months. The study was approved by the Institutional Review Boards of the Veterans Affairs Medical Centers in Portland, OR and Long Beach, CA, and all participants signed written informed consent.

Study design

Veterans with HCV and without major depressive disorder who were initiating antiviral therapy with pegylated interferon- α (PEG-IFN- α 2a: 135 mg/week or PEG-IFN- α 2b: 120 or 150 mg/week) and oral ribavirin (1000–1200 mg/day) were examined pretreatment (baseline) and then prospectively for the initial 16 weeks of therapy. Following baseline assessments and a blood draw, research participants were evaluated: 1) to identify the time course and development of psychiatric side effects during antiviral therapy, and 2) to determine the relationship among psychiatric symptoms, cytokines, and other factors putatively contributing to IFN-induced depression.

Psychiatric symptom and clinical assessments

Following informed consent, participants received: 1) a diagnostic psychiatric interview (i.e., SCID) [35] to assess lifetime and current history of psychiatric illness, including current and past drug use, 2) an assessment of current and past use of psychotropic medications, and family history of mood disorder, and 3) self-report questionnaires to complete: Beck Depression Inventory, Second Edition (BDI-II) [36] and Neurotoxicity

Rating Scale (NRS) [37]. After IFN therapy initiation, the BDI-II and NRS were administered every two weeks.

The BDI-II is a 21-item symptom inventory (scored from 0 to 4) that is reliable, valid, and commercially available [36]. In addition to BDI-II total scores, the Cognitive–Affective and Somatic factor scores derived from our recent BDI-II factor analysis [32] were also used to evaluate depressive symptoms in our participants before and during IFN therapy. The Cognitive–Affective factor consists of 11 BDI-II items and the Somatic factor consists of 7 items (Supplementary Table 1; see also Introduction). The BDI-II cutoff scores for general (14), cognitive–affective (7), and somatic (5) depression were based on: 1) the BDI-II manual recommendations for general depression [36] and 2) the ratio of BDI-II factor items to total items for cognitive–affective and somatic depression. For example, the cutoff on the BDI-II total score for the presence of depression symptoms is often set at 14 [36]. Since the maximum possible score for the total BDI-II is 84, a symptom severity ratio was calculated ($14/84=0.1666$). This ratio was multiplied by the maximum score on the Cognitive–Affective factor (11 items, $44 \times 0.1666=7.33$) and the maximum score on the Somatic factor (7 items, $28 \times 0.1666=4.66$) to calculate the respective cutoff scores. A similar strategy for classifying BDI-II depressive subtypes has been described in adolescent patients [38].

The Neurotoxicity Rating Scale (NRS) is comprised of 39 items, scored from 0 (“not present”) to 4 (“extremely severe”). The NRS is a reliable and valid self-report measure used in the evaluation of psychiatric and physical symptoms related to antiviral therapy, including depressed mood, difficulties with memory or concentration, fatigue, nausea or vomiting, body aches, fever, visual disturbances, bowel or bladder problems and joint pain [37].

Baseline viral loads, liver enzymes (i.e., aspartate aminotransferase; alanine aminotransferase), and platelet numbers were obtained via electronic medical records.

Blood sample collection

Participants were asked to provide blood samples at baseline and 16 weeks after the start of IFN therapy. Blood was collected in BD Vacutainer blood collection tubes (BD Diagnostics, Franklin Lakes, NJ) and separated via centrifugation. Plasma samples were stored at -80°C until assayed.

Enzyme-linked immunosorbent assays

Standard enzyme-linked immunosorbent assay (ELISA) kits were used to measure serotonin (sensitivity 5 ng/ml) and TNF- α (sensitivity 4 pg/ml). Samples were run in duplicate and assays were carried out according to manufacturer’s recommendations (Rocky Mountain Diagnostics, Colorado Springs, CO). Absorbance was measured at 450 nm using a BioRad Model 680 microplate reader (Bio-Rad Laboratories, Hercules, CA).

Statistical analysis

Wilcoxon signed rank tests were used to analyze the BDI-II total scores and factor scores at baseline and week 16. For between group analyses, we subdivided our sample into two groups: 1) patients who had an increase of 1 point or less on the Somatic factor from week 0

to week 2 (Low Somatic group, $n=12$) and 2) patients who had an increase of 2 points or greater on the BDI-II Somatic factor from week 0 to week 2 (High Somatic group, $n=18$). A 2-point increase on the Somatic factor of the BDI-II corresponded to a 7.1% increase in the presence or severity of somatic symptoms. Viral load, liver enzymes, platelet numbers, and TNF- α and serotonin levels were compared between groups using t-tests or Mann Whitney tests (when a non parametric approach was indicated). Statistical analyses were performed with Prism for Windows, version 4.03 (GraphPad Software, Inc., La Jolla, California). A significance level of $p<.05$ was used for all statistical tests.

Results

Depression outcomes during antiviral therapy

Table 1 summarizes the baseline demographic data and clinical characteristics for the total sample. Antiviral therapy with IFN resulted in a significant increase in total BDI-II scores from baseline (week 0; mean=4.24, S.D.=5.05) to week 16 (mean=7.07, S.D.=5.65) (Wilcoxon signed rank test; $p=.001$) (Fig. 1A). Two participants developed major depressive disorder during antiviral therapy and were treated with standard clinical care. The mean changes in total BDI-II scores from baseline (week 0) to weeks 2 through 16 are shown in Supplementary Fig. 1.

We applied our two factor HCV BDI-II model to assess the respective contributions of the Cognitive–Affective and Somatic factors to the IFN-induced increase in depressive symptoms [32]. There was no significant difference between Cognitive–Affective factor scores at week 0 (mean=0.10, S.D.=0.19), as compared with week 16 (mean=0.10, S.D.=0.18). However, the Somatic factor showed a significant increase from week 0 (mean=0.36, S.D.=0.40) to week 16 (mean=0.70, S.D.=0.46) ($p=.0006$). Somatic factor scores were higher than the Cognitive–Affective factor scores at all time points, showing a progressive increase through week 16 (Fig. 1B). Following the start of IFN therapy, peak BDI-II total scores were observed most often at weeks 2 and 16.

The highest BDI-II total score, Cognitive–Affective factor score, and Somatic factor score for all patients, with cutoff scores for general (14), cognitive–affective (7), and somatic (5) depression are reported in Supplementary Table 2. At baseline, 2.9% of patients exceeded BDI-II cutoff scores for general depression, 2.9% exceeded cutoff scores for cognitive–affective depression, and 26.5% exceeded cutoff scores for somatic depression. During the course of IFN therapy, 78.1% of patients exceeded BDI-II cutoff scores for somatic depression, whereas 22% and 6.3% exceeded the cutoff scores for general and cognitive–affective depression, respectively. Table 2 summarizes the percentage of patients exceeding cutoff scores for depression on the BDI-II total score, Cognitive–Affective factor score, and Somatic factor score from week 0 to week 16.

For validation, somatic symptoms were measured using the Neurotoxicity Rating Scale (NRS) and indicated a similar pattern of change during the course of therapy (Fig. 1C), with peak scores occurring as early as week 2 for some symptoms. The five NRS items shown correspond with the BDI-II items that comprise the Somatic factor (e.g., appetite changes,

concentration difficulty, tiredness/fatigue, and irritability) and exhibited increases over time that were consistent with the BDI-II Somatic factor (Fig. 1B and C).

Depression scores and TNF- α and serotonin levels before and during antiviral therapy

Given that the largest increase in somatic symptoms was seen two weeks after the start of IFN therapy, we subdivided our sample into two groups: 1) Low Somatic group (patients who had an increase of 1 point or less on the Somatic factor from week 0 to week 2, $n=12$) and 2) High Somatic group (patients who had an increase of 2 points or greater on the BDI-II Somatic factor from week 0 to week 2, $n=18$). The Low and High Somatic groups did not significantly differ from one another at baseline on the Somatic factor [means $\pm$ S.D.: 0.38 ± 0.43 vs. 0.36 ± 0.37 , respectively; $p=.87$ (Table 1)], but the groups were significantly different at week 2 (0.18 ± 0.05 vs. 0.92 ± 0.11 , respectively; $p<.0001$) (Fig. 2A). At week 0, patients in the High Somatic group had significantly higher levels of TNF- α , as compared to the Low Somatic group ($t=2.08$, $df=25$, $p=.048$) (Fig. 2B). Both of the patients who developed major depressive disorder during antiviral therapy were in the High Somatic group and correspondingly, had relatively high TNF- α levels at week 0 (8.60 pg/ml and 8.42 pg/ml). In contrast to TNF- α levels, the High Somatic group had significantly lower levels of serotonin at week 0, as compared to the Low Somatic group ($t=2.24$, $df=28$, $p=.033$) (Fig. 2C).

In the total sample of patients, 16 weeks of antiviral therapy marginally increased TNF- α levels, as compared to week 0 (means $\pm$ S.D.: 9.316 ± 7.492 pg/ml vs. 7.359 ± 5.197 pg/ml, respectively), but this difference was not statistically significant. The Low and High Somatic groups did not show significant between-group differences in TNF- α levels at week 16. Similarly, when comparing TNF- α levels at week 0 with those at week 16, there were no significant differences found between weeks 0 and 16 in either the Low or the High Somatic groups.

Consistent with our previous report [16], we found that in the total sample of patients, serotonin levels were significantly lower after 16 weeks of antiviral therapy, as compared to baseline (week 0) ($t=6.16$, $df=30$, $p<.0001$). The Low and High Somatic groups did not show significant between-group differences in serotonin levels at week 16.

To test whether the differences observed in baseline TNF- α or serotonin levels might be explained by differences in liver health status, we compared baseline viral load, liver enzymes, and platelets between Low and High Somatic groups. No significant between-group differences were found in any of the liver health variables tested.

Discussion

Recent studies in HCV [32,39], and clinical experiences suggest that depression may be better understood and treated if defined by pathophysiologically related depressive subtypes. Thus, the present study sought to prospectively evaluate the development of depressive symptoms in adults with HCV before and during antiviral therapy to determine their distinctive clinical features and biological correlates.

Consistent with previous reports [7,19,40], IFN therapy was accompanied by a significant increase in depressive symptoms, with neurovegetative and somatic symptoms of depression including changes in appetite, fatigue and irritability increasing within the first two weeks of IFN therapy. When the depressive symptoms were evaluated using our two-factor HCV BDI-II model derived from recent work [32], it became evident that the IFN-induced increases in BDI-II total scores were the result of significant increases in the Somatic factor, as the Cognitive–Affective factor did not change significantly following IFN therapy initiation. Similarly, a greater percentage of patients scored higher than the cutoff scores for somatic as compared to cognitive–affective depression (78.1% vs. 6.3%, respectively).

Pre-clinical and clinical studies have increased our understanding of how IFN affects neurochemical pathways putatively involved in the etiology of depression, including the serotonergic system, hypothalamic–pituitary–adrenal (HPA) axis, and the cytokine network [41,42]. Emerging evidence further suggests that the hepatitis C virus itself may directly contribute to increased immune activation and pro-inflammatory cytokine expression in the central nervous system. Hepatitis C viral sequences and proteins have been found in brain macrophage/microglia cells, and activation of these brain cells in HCV-infected patients is associated with higher expression of mRNA transcripts for key immune activation cytokines (e.g., IL-1 and TNF- α) than in HCV-negative control patients [43].

We found that patients who reported the greatest increases in somatic symptoms from baseline to week 2 had significantly higher levels of TNF- α and lower levels of serotonin at baseline, as compared to patients with minimal or no increase in somatic symptoms. These findings are consistent with other reports, as persistent pro-inflammatory cytokine mRNA levels, including TNF- α , following the start of IFN therapy are associated with the development of significant symptoms of depression during therapy [29]. Similarly, a polymorphism in TNF- α [involved in high production of this pro-inflammatory cytokine [44,45]], appears to influence fatigue and irritability in patients with HCV [46]. Recently, somatic symptoms of depression were independently associated with increased sTNFR2 levels in patients with heart failure [47]. Another study found that adults with higher-expressing allele variants of the serotonin transporter gene (L'L' and L'S') reported significantly more somatic symptoms in the last two years than those with lower-expressing variants (S'S') [48]. Thus, some genetic factors may increase the likelihood of developing somatic symptoms, while other genetic factors (e.g., brain-derived neurotrophic factor) may contribute more to cognitive–affective symptoms [49].

The somatic symptoms of depression are often not responsive to antidepressant treatment [50] and may result in a more chronic course of illness [51]. When present, somatic symptoms can both interfere with successful continuation of IFN-based therapy and with quality of life [11,52,53]. Unfortunately, there are limited evidence-based treatment recommendations for managing these somatic symptoms in HCV patients, as the pathophysiological mechanisms are still being investigated. To our knowledge, our study is the first to explore the role of inflammatory and serotonergic mechanisms associated with depressive subtypes in patients with HCV undergoing antiviral therapy.

A strength of the study was its prospective design, with multiple time points, and use of a well-validated and commonly administered measure of depressive symptoms. The study was limited: 1) by a relatively small sample size, which affected our ability to detect depressive symptoms, and 2) by the possibility that hemolytic anemia (induced by ribavirin) could have contributed to increased somatic symptoms during antiviral therapy. In addition, the majority of patients were male Veterans; thus, we do not know how representative our sample was of the HCV outpatient population as a whole.

Over the past 15 years, significant advancements have been made in the treatment of HCV as well as the management of side effects accompanying IFN-based therapies. As a result of this productivity and new information, we now know that patients with diagnoses of major depressive disorder should not necessarily be excluded from treatment [54]. Screening and monitoring of neuropsychiatric symptoms during the course of therapy are strongly recommended [2,55]. Collectively, these research efforts have helped to remove barriers to treatment and have led to an increased number of patients potentially eligible for HCV treatment [56]. Although we have a better understanding of the time course, phenomenology, and biochemical mechanisms of IFN-induced neuropsychiatric impairments, particularly depression, new interventions to manage adverse somatic effects are needed, as these side effects may increase with the use of the newly available direct acting antiviral therapies, which now include the protease inhibitors, boceprevir or telaprevir [57].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Beck Depression Inventory-II (BDI-II) and Neurotoxicity Rating Scale (NRS) scores for 32 patients across 16 weeks of antiviral treatment for HCV. Average BDI-II total scores (A) and average item scores on the Cognitive–Affective and Somatic factors (B) are plotted across weeks. Somatic symptoms measured using the NRS show a similar pattern of change during the course of IFN therapy (C). The five NRS items shown correspond with the BDI-II items that comprise the Somatic factor [36].

Fig. 2.

Baseline TNF- α and serotonin levels as risk factors for increased somatic symptoms during IFN therapy. Patients who reported an increase in somatic symptoms after two weeks of IFN therapy (High Somatic group) were compared with patients who did not report an increase in somatic symptoms (Low Somatic group) (A). The High Somatic group had significantly higher levels of TNF- α (B) and significantly lower levels of serotonin (C) at baseline, prior to the start of IFN therapy.

Table 1

Baseline demographic and clinical information for 32 patients who underwent interferon-based therapy for HCV

Variable	Mean	Standard deviation
Age	39.32	15.26
HCV viral load	1,974,338	2,096,932.10
HCV viral load (IU/mL)	1,230,000 (median)	74,223–7,000,000 (range)
AST	66.08	36.76
ALT	103.44	80.04
Platelets	194.20	58.41
Tiredness/Fatigue—total sample ^a	1.81	0.78
Low Somatic group	1.917	0.67
High Somatic group	1.733	0.70
BDI-II Somatic factor—total sample ^b	0.37	0.39
Low Somatic group	0.38	0.43
High Somatic group	0.36	0.37
	<i>N</i>	%
Male gender	30	93.75
Female gender	2	6.25
Race		
Caucasian	27	84.38
Other	5	15.63
History of MDD	0	0
HCV genotype		
1	11	34.38
2	16	50.00
3	2	6.25
4	1	3.13
Unknown	2	6.25

Abbreviations: AST = aspartate aminotransferase; ALT = alanine aminotransferase; IU = International Units; MDD = major depressive disorder.

^aTiredness/Fatigue is measured by a single item on Neurotoxicity Rating Scale (NRS). When comparing patients in the Low Somatic group with those in the High Somatic group, there were no significant baseline differences on Tiredness/Fatigue, as evaluated by t-test.

^bThe Somatic factor of the BDI-II consists of 7 items (i.e., loss of energy, changes in sleeping pattern, irritability, changes in appetite, concentration difficulty, tiredness or fatigue, loss of interest in sex). T-test did not detect a significant baseline differences between the Low and High Somatic groups on the BDI-II Somatic factor.

Table 2

Percentage of patients exceeding cutoff scores for depression on the BDI-II total score, Cognitive–Affective factor score, and Somatic factor score

	BDI-II total score ^a	Cognitive–Affective factor score ^b	Somatic factor score ^c
Week 0	2.9	2.9	26.5
Week 2	16.1	3.2	35.5
Week 4	9.7	3.2	38.7
Week 6	14.3	3.6	35.7
Week 8	13.3	0	53.3
Week 10	7.4	0	37.0
Week 12	13.3	3.3	46.7
Week 14	7.4	3.7	37.0
Week 16	9.7	6.5	48.4

^a Cutoff 14.

^b Cutoff 7.

^c Cutoff 5.