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Development of a Clinician-Administered National Institutes of Health-Brief Fatigue Inventory: a Measure of Fatigue in the Context of Depressive Disorders

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Abstract

Objective—Fatigue is a complex, multidimensional condition. Although it is often associated with depression, it is not known whether it has a distinct network from depression or whether it can be clinically evaluated, separately. This study describes preliminary findings in the development of a brief, clinician-administered instrument to measure fatigue in the context of depressive disorders using items from existing clinician-administered depression and mania scales.

Methods—Based on items from prior fatigue measurements, items were selected from the Hamilton Depression Rating Scale (HDRS), Montgomery-Asberg Depression Rating Scale (MADRS), Young Mania Rating Scale, and Structured Interview Guide for HDRS with Atypical Depression. The final items composed the NIH-Brief Fatigue Inventory (NIH-BFI). Responses from 89 depressed adults collected pre- and post-antidepressant therapy (ADT) determined the reliability and consistency of the NIH-BFI using Cronbach's alpha and principal components analysis (PCA). Correlations of the NIH-BFI and fatigue items from other scales before and after ADT explored validity.

Results—The 7-item NIH-BFI had Cronbach alphas ranging from 0.81–0.88 and PCA indicating a single dimension. The NIH-BFI score was strongly correlated ($r=0.73$, $p<0.001$) with fatigue items from Beck Depression Index, with MADRS without fatigue items ($r=0.77$, $p<0.001$), and HDRS without fatigue items (pre: $r=0.69$, $p<0.001$).

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Conflicts of Interest

The authors have reported no potential conflicts of interest.

Contributors

Conceived and designed the experiments: CZ. Analyzed the data: DL, ES. Wrote the first draft of the manuscript: LS. Contributed to the writing of the manuscript: LS, DL, ES, RMV, CZ. Agree with manuscript results and conclusions: LS, DL, ES, RMV, CZ. Jointly developed the structure and arguments for the paper: LS, RMV, DL. Made critical revisions and approved final version: CZ. All authors reviewed and approved of the final manuscript.

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Conclusions—Preliminary findings show support for internal consistency reliability and validity of the NIH-BFI, a clinician-administered measure of fatigue. Further testing in other clinical populations is recommended to obtain additional information on reliability and validity. The NIH-BFI provides a method for clinician-rated fatigue that may be a separate from depression.

Keywords

fatigue; depression; clinician-administered scale; instrument development

Introduction

Fatigue is defined as a subjective sense of persistent tiredness or loss of energy that interferes with the performance of daily life activities and is not relieved by rest [1]. However, this pervasive and debilitating clinical condition is still defined with suboptimal consistency [2–5]. Evidence suggests that fatigue is often associated with depression in individuals with Axis I psychiatric disorders [6, 7], as well as in those with multiple sclerosis [8], sarcoidosis [9], and cancer [10]. Oncology patients experiencing fatigue also report symptoms of depression such as a sense of hopelessness, worthlessness, guilt, and suicidal ideation [11]. The strong association between fatigue (total or general, physical, and mental) and depressive symptoms [12], makes it challenging to obtain measurements that distinguish one from the other [13].

It is suggested that the relationship of fatigue and depression may explain mutual psychological and shared neuroanatomical pathways between these two clinical conditions [14]. Presence of fatigue or loss of energy is one of the core symptoms for the major depressive disorder (MDD) diagnosis [15]. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for MDD describes fatigue or loss of energy as a physical manifestation [15]. However, fatigue is believed to be multidimensional and includes both physical and psychological (mental or emotional) domains [16]. Physical fatigue is often associated with the reduction of muscle contractions from impaired energy resources [17], while psychological fatigue is associated with affective, behavioral, and cognitive impairments [17, 18].

Although fatigue and depression are strongly associated, there is empirical evidence that they are also distinct entities. Two different studies found that fatigue continued after depression was in remission. Up to 35% of patients with MDD who achieved remission continued to report persistent fatigue [10]. In another study, approximately 40% of patients with partial or full remission of MDD after antidepressant therapy still reported persistent physical fatigue [19]. These studies affirm that fatigue and depression are not always linked, which suggests that measures should be able to differentiate them.

There are several valid, self-report measurements to assess fatigue diagnosis and severity, however, the validity of these instruments is often questioned, especially when used as a diagnostic tool for psychiatric patients actively experiencing overlapping symptoms related to their conditions [20, 21, 22]. The heavy reliance on clinician-administered questionnaires in the mental health field to diagnose psychiatric conditions is influenced by the idea that

individuals with psychiatric illness have impaired ability to accurately judge their competence in several quality of life domains, such as social interactions, work performance, and self-care [23], all necessary domains in the assessment of fatigue. Previous reports showed that poor insight and awareness of individuals to their psychiatric illness contribute to poorer ratings of social function and physical performance [24, 25]. For example, increasing concerns are raised that overreliance on self-report questionnaires can lead to overdiagnoses or underdiagnoses of psychiatric conditions [20, 21, 26]. A recent report suggested that the use of clinician-administered probing can provide more sensitive indicators for diagnosing psychiatric disorders [23], and data obtained from clinician-administered assessments can measure severity of depressive symptoms more accurately than self-report [27, 28]. Considering that fatigue items are included in several clinician-administered depression instruments, a clinician-administered fatigue questionnaire could be developed by extracting these items and exploring their reliability and validity to distinguish fatigue from the other symptoms, such as depression.

Recently, a single-item, clinician-administered fatigue questionnaire obtained from the Clinical Global Impression scale was used to assess fatigue in psychiatric patients [29]. This scale showed good psychometric properties when compared with the Massachusetts General Hospital Cognitive and Physical Functioning Scale [30]. However, in addition to the limitation of being a single-item scale, there was inadequate support for its validity, especially the lack of studies comparing it with more established self-report fatigue scales [31]. Hence, there is a need to develop a brief, multiple-item tool that can fully assess the concept of fatigue and also be administered by clinicians in practice.

This paper introduces preliminary findings on a clinician-administered scale aimed to measure rapid change in fatigue based on responses obtained from a clinical trial investigating the rapid effect of ketamine on depression. This scale has the potential to be useful in both clinical practice and research. We also explored whether the preliminary findings can provide information on whether this newly developed scale could efficiently evaluate fatigue separately from depression.

Methodology

Design and subjects

All patients included in the analyses were from a series of National Institutes of Health (NIH), institutional review board-approved National Institute of Mental Health (NIMH) clinical studies exploring the efficacy of ketamine as an intervention in reducing depressive symptoms. Informed consents were obtained before study measures were obtained. All of these studies were conducted at the NIH Clinical Center, Bethesda, Maryland.

The presence of clinical depression, based on DSM-IV criteria, was established as the eligibility criterion for participation in these clinical trials. Questionnaire responses at pre- and 230 minutes post-intervention were used in the analyses, because significant improvements in depressive symptoms were observed between these time points in previous reports [32, 33]. The strong association of fatigue with depression [12], enabled us to expect that the improvements in the levels fatigue would also be correlated with significant

improvements in depressive symptoms as observed in a previous study, starting a day following ketamine infusion [32].

Procedures for Item Generation

Items pertaining to the concept of fatigue were selected by NIH-credentialed mental health nurses and psychologists experienced in administering existing clinician-administered psychiatric scales used in NIMH clinical trials (i.e., Hamilton Depression Rating Scale [HDRS], Montgomery-Asberg Depression Rating Scale [MADRS], Young Mania Rating Scale [YMRS], and Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression [SIGH-SAD]) to develop a clinician-administered NIH-Brief Fatigue Inventory (NIH-BFI). The psychometric properties of these psychiatric scales from which the NIH-BFI items were selected are as follows:

MADRS—The MADRS is a 10-item, unidimensional instrument used to evaluate psychological aspects of depressive symptoms in adults [34]. A previous psychometric study evaluating the use of MADRS in clinical practice revealed very good internal consistency reliability with a Cronbach's alpha of 0.85 [35], very high correlations among all items ($r=0.95$) [36], good concurrent validity with Pearson's correlation coefficient of 0.81 between the MADRS clinician-administered score and the MADRS self-administered score, and sensitivity to change over a 4-week observation period with correlations of 0.71 between change in scores [35]. The inter-rater reliability ranged from 0.89–0.97 [34]. Each of the 10 items is rated on a scale of 0 to 6, with specific descriptors for each item. These individual item scores are added together to form a total score, which can range between 0 and 60 points. A higher total score reflects greater depressive symptoms.

HDRS—The 17-item version is a widely used multidimensional, observational rating measure of depression severity [37]. It assesses both the presence and severity of individual signs and symptoms characterizing depression without psychotic features. A higher total score reflects greater depressive symptoms. Psychometric properties of this scale include an internal consistency reliability of 0.83 and median item-total correlation of 0.46 [38]. Inter-rater reliability is reported at 0.80–0.98 [39]. Test-retest reliability is reported at 0.81, even among minimally trained raters from multiple disciplines [40].

SIGH-SAD—This scale is a supplemental section of the HDRS that includes eight symptoms of atypical depression [41, 42]. It was designed for general use in depression research and clinical evaluation, regardless of seasonality. Scores range from 0 to 88 with higher scores reflecting greater depression severity. Reliability for scale items of the SIGH-SAD as measured by Cronbach's alpha was established to be 0.87 [42].

YMRS—The YMRS is an 11-item scale that measures symptoms of hypomania and mania. Items 5, 6, 8, and 9 are rated on a scale from 0 (symptom not present) to 8 (symptom extremely severe) [43]. Remaining items are rated on a scale from 0 (symptom not present) to 4 (symptom extremely severe). The YMRS total score ranges from 0 to 60, with a greater total score reflecting more severe manic symptoms. Inter-rater reliability is 0.93 and correlations between individual items ranged from 0.41–0.85 [43].

Beck Depression Inventory (BDI)—The BDI is a 21-question, widely-used, validated, multiple-choice, self-report inventory of the characteristic attitudes and symptoms of depression [44]. Scores from the fatigue items from this self-administered scale were used to determine validity of the NIH-BFI score pre- and post-intervention.

Data Analyses

Initial analyses of the psychometric properties of the NIH-BFI were determined using descriptive statistics, Cronbach's alpha, Pearson's correlations, principal component analysis (PCA), and intra-class correlation (ICC). ICCs were calculated with each model for individual measures to facilitate understanding whether a single item would provide similar reliability to the average value for all of the items. A consistency model was used for this calculation given that individual items have different ranges.

Results

Sample

A group of 89 participants diagnosed with Major Depressive Disorder (MDD, $N=55$) or Bipolar Disorder (BD, $N=34$) enrolled in NIMH clinical trials were examined to determine if the total NIH-BFI score reported by these participants was stable and reproducible with repeated measurements. Table 1 describes the sociodemographic and clinical characteristics of the sample. The mean age of the participants was 47.0 (± 12.1 [SD]) years, 54% were men, and their mean length of illness was 27.7 (± 12.9) years. About 70% of the participants had a prior psychiatric hospitalization, 58% had comorbid anxiety disorder, and 89% had a family history of mood disorders. MDD participants were not taking any psychiatric medications, but BD patients were on stable doses of either lithium or valproate during the entire study.

Item Selection and Content Validity

A total of 10 items with >3 rating were initially selected. From the HDRS, items reflecting agitation, general somatic symptoms, motor retardation, and work and activities were used, one fatigability item was selected from the SIGH-SAD. Items included from the MADRS included those related to concentration difficulties and lassitude. Finally, items on motor activity, irritability, and speech problems were incorporated from the YMRS. These selected items were similarly worded to items of other reliable, validated, and widely used fatigue measures such as the 13-item Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) subscale, 7-item Patient Reported Outcomes Measurement Information System (PROMIS) – fatigue short form, and the 27-item, multidimensional revised Piper Fatigue Scale (rPFS)(see Supplemental Table).

Internal Consistency Reliability

The 10 initial items were included in calculating the Cronbach's alpha to determine whether these items fit into a coherent construct. Alphas were examined with individual items deleted to determine whether specific items decreased the coherence of the underlying construct. In addition, Pearson correlations among individual items were examined to determine whether individual items were related to other fatigue symptoms. If an item had

low correlations with other items and it reduced the coefficient alpha substantially, then it was removed from the total fatigue item list before the process was repeated. The process was continued until no substantial decrease in alpha occurred with item deletion. The final list of symptoms was labeled the NIH-BFI.

In the initial examination of Cronbach's alpha, there was no variation in the motor activity item from the YMRS, so that item was dropped from further analysis. Then, Cronbach's alpha from the next model was 0.84. Although eliminating any individual item did not substantially increase alpha, the speech item from the YMRS and the agitation item from HDRS were dropped because they had low correlations ($r=-0.11$ to 0.26) with the other items. For the final 7-item model, the Cronbach's alpha was 0.87, which suggested a coherent construct among the items and the inter-item correlations ranged between 0.78 and 0.88 (Table 2). Further, the ICC for a single observation from this model was 0.49. Because Cronbach's alpha is equivalent to the ICC for the average of a set of items, this illustrates that using a subscale with several items would provide a more reliable measure of the construct than using an individual item.

A principal component analysis (PCA) with varimax rotation was used to examine whether the final items composed a single construct or whether the list might include multiple latent constructs. Factors with eigenvalues greater than one were accepted. A PCA indicated a single component underlying the seven items that explained 59% of the variance in the items. The MADRS item for lassitude had the highest factor loading (0.94) and the SIGH-SAD item for fatigability had the second highest (0.88). Because these two items appear to be the most directly fatigue-related questions, the likelihood that the underlying construct measures fatigue appears strong. The HDRS item for motor retardation had the lowest loading (0.55). Commonalities for five of the items were 0.50 or greater. The commonalities were lower for YMRS irritability (0.34) and HDRS motor retardation (0.30). After calculating the sum of the items, the total fatigue scores ranged from 0 to 24. The variable appeared to be normally distributed based on the Kolmogorov-Smirnov test ($p=.20$) with an average score of 11.6 ($SD=6.5$).

Validity

To assess the validity of NIH-BFI, we examined whether the total NIH-BFI score would converge with other subjective measures of fatigue assessed over time, within the context of depression. We found that post-intervention, the total NIH-BFI score had a moderate to strong correlation with the self-reported fatigue item from the BDI item #17: 0=I don't get more tired than usual, 1=I get tired more easily than I used to, 2=I get tired from doing almost anything, 3=I am too tired to do anything; $r=0.73$, $p<0.001$). Further, total NIH-BFI score also showed a moderate to strong correlation with BDI item #15 (0=I can work about as well as before, 1=It takes an extra effort to get started at doing something, 2=I have to push myself very hard to do anything, 3=I can't do any work at all; $r=0.66$, $p<0.001$).

The relationship of fatigue and depression [12, 13] is supported by the strong association of NIH-BFI with measures of depression at both time periods. The NIH-BFI total score was correlated with the MADRS (pre: $r=0.47$, $p<0.001$; post-intervention: $r=0.77$, $p<0.001$); and HDRS scores (pre: $r=0.28$, $p=0.02$; post-intervention: $r=0.69$, $p<0.001$). However, a decline

in the association of depression and fatigue was observed when specific NIH-BFI items (lassitude, fatigability) were examined against depression-specific items (MADRS reported sadness item: $r=0.59$ [lassitude], $r=0.52$ [fatigability], $p<0.001$; and HDRS depressed mood item: $r=0.56$ [lassitude], $r=0.49$ [fatigability], $p<0.001$). This smaller association of NIH-BFI fatigue-specific items with depression-specific items suggests that fatigue can be assessed separately from depression (Table 3).

Discussion

Fatigue is currently measured almost exclusively by self-report instruments, and there is no validated clinician-administered instrument to provide an objective assessment of fatigue. This study describes the preliminary findings in the development of a clinician-administered fatigue rating scale using fatigue items from existing clinician-administered depression and mania scales. Items were selected based on their ability to measure the concept of fatigue by four fatigue researchers. The NIH-BFI is a new 7-item scale, and initial psychometric analyses show that it has Cronbach alphas ranging from 0.81–0.88 and PCA indicating a single dimension (Table 4). The NIH-BFI score was strongly correlated ($r=0.73$, $p<0.001$) with fatigue items from BDI before and after antidepressant therapy.

Our findings affirm the strong association of fatigue and depression [12, 13], as shown in the improvement of the correlation between fatigue and depression post-intervention suggesting a shared physiological mechanism. However, the NIH-BFI scores can be discriminated from other depression scales without the fatigue items ($r=0.68$ – 0.77 , $p<0.001$, table 3). Specifically, the lassitude and fatigability NIH-BFI items have slightly lower correlations with depression without fatigue ($r=0.49$ – 0.66 , $p<0.001$, table 3) compared to the total NIH-BFI score. These two NIH-BFI items have the highest loadings on the PCA (0.94 and 0.88, respectively; table 2), which suggests that these items are the most representative of the fatigue construct. Using only these two NIH-BFI items is an interesting idea. They may offer a construct more orthogonal to depression, but the score may be less stable with a smaller number of items. The association of fatigue and depression is complex and continued use and improvement of this instrument to serve as a unique measure of fatigue separate from depression is warranted.

Having a reliable and valid scale for fatigue could assist in the examination of the relationship between depression and fatigue in both clinical and research settings. Therefore, extending the use of NIH-BFI to normal controls or other clinical populations where fatigue is a major complaint can provide further support for its reliability and validity as a measure that can distinguish fatigue from depression. The NIH-BFI is a unique tool to become a pioneering clinician-administered measure of fatigue in the context of depression; hence, advancing the science especially addressing the concerns related to self-reporting bias raised by clinicians after observing discrepancies in self-report and clinician-administered psychiatric tools. One major limitation of our preliminary findings is the lack of attributional component of the final items of the NIH-BFI. Because the final NIH-BFI items were selected based on their inter-item associations with the internal consistency analyses after they were collected, the NIH-BFI scores do not reflect whether they are related solely to the

experience of fatigue or from symptoms related to depressive disorders. Further, test-retest reliability could not be determined in the current study.

Fatigue is described as a multidimensional construct consisting of physical, cognitive, and emotional domains [45]. The NIH-BFI characterized the different domains of fatigue by incorporating items that measured physical, cognitive, and emotional domains of fatigue. The physical domain of fatigue is measured by NIH-BFI in items that assess lassitude, general somatic symptoms, and work/activities. Items assessing concentration, listlessness and indecision with regard to work and activities measure the cognitive domain of fatigue. The fatigability item captures the emotional domain by probing feelings of being tired and energy level. These different fatigue domains as measured by the NIH-BFI items also used terms similar to those used in items from established, validated measures of related fatigue concepts such as the Rothschild Scale for Antidepressant Tachyphylaxis® (RSAT) and the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) [46, 47] (see Supplemental Table). Our findings also indicated that the total NIH-BFI score is stable in measuring fatigue, when it showed moderate to strong correlations with specific physical, cognitive, and emotional symptoms (e.g., lassitude, concentration, fatigability, sadness, and depressed mood) as measured by items from established self-report and clinician-administered depression and mania scales. To validate if the NIH-BFI truly assesses the multidimensional construct of fatigue, comparison of NIH-BFI scores with fatigue scores from other valid, multidimensional fatigue scales including the RSAT and CPFQ should be pursued [46, 48]. Validity and reliability of the NIH-BFI overtime is also necessary to investigate.

The etiology of fatigue is thought to involve various mechanisms. Several imaging studies showed that glial activation and oxidative stress marked by structural changes (e.g., cortical thickness) and changes in chemical profiles (e.g., lactate) of certain areas of the brain were observed in fatigued patients [49, 50]. We recently reported a unique genomic signature of fatigue from men who complained of worsening fatigue, but with very low HDRS scores, while receiving localized radiation therapy for non-metastatic cancer [51, 52]. Functional network analyses of these differentially expressed genes revealed that these genomic fatigue signatures were associated with neuroinflammation and metabolism, mechanisms proposed as etiology of fatigue [53, 54].

Our recent genomic findings and the development of this valid measure of fatigue strengthens our conclusion that fatigue can be measured separately from depression. Our findings suggest that NIH-BFI is useful to distinctly measure fatigue because it only overlaps about 50% with common measures of depression. Further exploration of the validity of the NIH-BFI in other clinical populations should increase our understanding of what is different about depression and fatigue.

Conclusions

These preliminary results show that the NIH-BFI is a concise, reliable, and valid clinician-administered measure of fatigue. Although these are initial results, the psychometric properties of NIH-BFI are uniquely useful for measuring fatigue separately from depression.

Testing of test-retest reliability is recommended, further validation is warranted using other clinical populations, and comparisons of the NIH-BFI with other multidimensional fatigue scales is needed because of the complex nature of the association of fatigue with depression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Acronyms

ADT	antidepressant therapy
BDI	Beck Depression Inventory
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECT	Electroconvulsive Therapy
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
HDRS	Hamilton Depression Rating Scale
ICC	intra-class correlation
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	major depressive disorder
NIH	National Institutes of Health
NIH-BFI	National Institutes of Health-Brief Fatigue Inventory
NIMH	National Institute of Mental Health
PCA	principal component analysis
PROMIS	Patient reported Outcomes Measurement Information System
PTSD	Post Traumatic Stress Disorder
rPFS	revised Piper Fatigue Scale
SIGH-SAD	Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression
SD	standard deviation

YMRS

Young Mania Rating Scale

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Highlights

- The NIH-BFI is a concise, reliable, and valid multidimensional, clinician-administered measure of fatigue.
- The NIH-BFI is useful for conducting research and in determining outcomes for clinical interventions because it can evaluate fatigue within the context of depression.
- The NIH-BFI is useful to distinctly measure fatigue because it only overlaps about 50% with common measures of depression.

Table 1Sociodemographic and clinical characteristics of the sample ($N=89$).

Characteristics	Mean	SD
Age	47.0	12.1
Age of Onset (Years)	19.3	10.7
Length of Illness (Years)	27.7	12.9
Length of Current Episode (Months)	59.2	101.7

Characteristics	<i>n</i>	%
Sex (Male)	48	54
Education		
Graduate Professional Degree	28	32
College Graduate	24	27
Some College	23	26
High School or Less	14	16
Diagnosis		
Bipolar Disorder	34	38
Major Depressive Disorder	55	62
Depression Subtype		
Atypical	21	25
Melancholic	29	34
Other	34	40
Illness History		
Psychiatric Hospitalization	61	70
Suicide Attempt	36	41
ECT Exposure	36	41
Comorbidity		
Anxiety Disorder	51	58
PTSD	10	11
Psychosis	10	23
Alcohol Abuse	37	42
Substance Abuse	39	44
Family History		
Alcohol Dependence (First Degree)	33	37
Mood Disorder	79	89
Anxiety Disorder	12	27
Suicide	26	33

ECT = Electroconvulsive Therapy, PTSD = Post Traumatic Stress Disorder

Table 2

Internal Consistency Reliability and PCA for Final 7 items

	Cronbach's Alpha	PCA
	Final Model	Loading
MADRS: Concentration Difficulties	0.84	0.80
MADRS: Lassitude	0.81	0.94
SIGH-SAD: Fatigability	0.83	0.88
YMRS: Irritability	0.87	0.58
HDRS: Work and Activities	0.85	0.74
HDRS: General Somatic Symptoms	0.85	0.81
HDRS: Retardation	0.88	0.55
Cronbach's Alpha (All items)	0.87	
ICC - Consistency (Single item)	0.49	

Hamilton Depression Rating Scale (HDRS), Montgomery-Asberg Depression Rating Scale (MADRS), Young Mania Rating Scale (YMRS), Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression (SIGH-SAD), Intra-Class Correlations (ICC)

Table 3

Correlations of Fatigue and Depressive Symptoms using different scales and items.

Correlations					
	NIH-BFI		MADRS: Lassitude		SIGH-SAD: Fatigability
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>p</i>
MADRS without Fatigue	0.77	<0.001	0.66	<0.001	<0.001
MADRS: Reported Sadness	0.69	<0.001	0.59	<0.001	<0.001
MADRS: Concentration Difficulties	0.83	<0.001	0.70	<0.001	<0.001
HDRS without Fatigue	0.69	<0.001	0.58	<0.001	<0.001
HDRS: Depressed Mood	0.68	<0.001	0.56	<0.001	<0.001
HDRS: Work and Activities	0.73	<0.001	0.61	<0.001	<0.001
HDRS: General Somatic Symptoms	0.77	<0.001	0.80	<0.001	<0.001
HDRS: Retardation	0.54	<0.001	0.47	<0.001	<0.001
BDI: Loss of Energy	0.66	<0.001	0.57	<0.001	<0.001
BDI: Irritability	0.73	<0.001	0.72	<0.001	<0.001
YMRS: Irritability	0.63	<0.001	0.44	<0.001	<0.001

National Institutes of Health – Brief Fatigue Inventory (NIH-BFI), Hamilton Depression Rating Scale (HDRS), Montgomery-Asberg Depression Rating Scale (MADRS), Young Mania Rating Scale (YMRS), Beck Depression Inventory (BDI), Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression (SIGH-SAD)

Table 4

The National Institutes of Health - Brief Fatigue Inventory

Item	Description
Concentration difficulties	How has your memory been this past week? Do you have difficulty concentrating or collecting your thoughts? Reading? Watching TV? Holding a conversation? Difficulty getting started? Simple activities like daily routines? How about minor decisions? Have you been getting easily distracted? 0 = no difficulties in concentrating 1 2 = occasional difficulties in collecting one's thoughts 3 4 = difficulties in concentrating and sustaining thought, which reduces ability to read or hold a conversation 5 6 = unable to read or converse without great difficulty
Lassitude	How has your energy been this past week? Feeling tired? Fatigued? Do you notice getting tired more easily? Has it been difficult to get started on things you need to do? Including simple routines? No motivation to do anything? (more affective fatigue) 0 = hardly any difficulty getting started; no sluggishness 1 2 = difficulties in starting activities 3 4 = difficulties in starting simple routine activities, which are carried out with effort 5 6 = complete lassitude; unable to do anything without help
Fatigability	How has your energy been this past week? Do you feel heavy? Heaviness on limbs? Leadiness? Weighed down? Started doing physical tasks but unable to finish because of being tired? How many times a day do you feel tired? How often a day? How often a week? (more physical fatigue) 0 = does not feel fatigued more than usual 1 = feels more fatigued than usual but this has not impaired function significantly; less frequent than in (2) 2 = more fatigued than usual; at least one hour a day; at least three days a week 3 = fatigued much of the time most days 4 = fatigue almost all the time
Irritability	Have you been feeling especially tense or irritable this past week? Edgy? Worried a lot about things you don't ordinarily worry about? Unable to relax? Easily tearful? Startle easily? Restless? ** Rating below requires both observation and patient report. 0 = absent; reports not tensed or irritated 2 = looks anxious, worried, or tearful at times during interview; reports some episodes of being tensed or irritable 4 = irritable at time during interview; reports recent episodes of anger or annoyance 6 = frequently irritable during interview; short, curt throughout 8 = hostile, uncooperative; interview impossible
Work and activities	How have you been spending your time this past week? Have you been working? Have you been social as when you feel well? Have you stopped doing anything you used to do? How would you describe your level of interest and motivation to complete daily activities? 0 = no difficulty 1 = thoughts and feeling of incapacity, fatigue or weakness related to activities, work, or hobbies 2 = loss of interest in activity, hobbies, or work by direct report of the patient or indirect revealed by listlessness, indecision, and vacillation (feels he has to push self to work or do activities) 3 = decrease in actual time spent in activities or decrease in productivity 4 = stopped working because of present condition
General somatic symptoms	During the past week, have you had any heaviness in limbs, back or head: backaches, headache, muscle aches; loss of energy and fatigue 0 = none 1 = heaviness in limbs, back or head; backaches, headaches, muscle aches; loss of energy and fatigue 2 = any clear-cut symptom
Retardation	Observe slowness of thought and speech, impaired ability to concentrate, decreased motor activity 0 = normal speech and thought 1 = slight retardation at interview 2 = obvious retardation at interview 3 = interview difficult 4 = complete stupor
Total Score	