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The Relation of Illness Perceptions to Stress, Depression, and Fatigue in Patients with Chronic Lymphocytic Leukemia

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Abstract

Objective—Chronic lymphocytic leukemia (CLL) is the most prevalent adult leukemia and is incurable. The course and treatment of CLL is unique and characterized by repeated cycles of treatment, stable disease, and relapse. Utilizing a Self-Regulatory Model framework (Leventhal et al., 1980), we examined the relationship between patients' illness perceptions and cancer-specific stress, depression, and fatigue. Our aim was to test illness perceptions as predictors of these outcomes when variance due to disease and treatment variables was controlled.

Design—Data were collected on 147 patients with relapsed/refractory CLL as they entered a phase-II clinical trial of an investigational medication at a university affiliated, National Cancer Institute designated comprehensive cancer center.

Main outcome measures—Cancer-specific stress, depressive symptoms, and fatigue interference.

Results—Hierarchical multiple regression was used. Consequences and emotional representation were related to all outcomes (ps <.01). Illness concern was related to cancer-specific stress (p <.01), and identity was related to fatigue interference (p <.01). All relationships were observed while controlling for number of previous CLL therapies received.

Conclusion—Illness perceptions are related to cancer-specific stress, depressive symptoms, and fatigue interference in relapsed/refractory CLL. Interventions targeted at restructuring maladaptive illness perceptions may have clinical benefit in this population.

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Keywords

chronic lymphocytic leukemia; illness perceptions; stress; depression; fatigue

Introduction

There is variability in psychological and physical outcomes of patients with chronic illness, even among those with the same disease. Markers of disease severity do not always account for these differences (Rozema, Vollink, & Lechner, 2009). Leventhal's Self-Regulatory Model of Illness Behavior (Leventhal, Meyer, & Nerenz, 1980) provides a theoretical framework for conceptualizing how individual differences may arise. The Self-Regulatory Model proposes that in response to a health threat such as a new physical symptom or sign, individuals construct an internal network of beliefs (i.e., illness perceptions) having cognitive and emotional content. One's perception of their illness guides self-care and coping and influences psychological and physical disease outcomes.

Rather than a single "perception," there are *dimensions* along which patients perceive illness (Leventhal, Nerenz, & Steele, 1984; Broadbent, Petrie, Main, & Weinman, 2006), namely, dimensions of "consequences," "emotional representation," "identity," "concern," "personal control," "treatment control," "coherence," and "timeline". Early research examined patients' illness perceptions using open-ended interviews to determine the nature of each (Leventhal & Nerenz, 1985). As research progressed, self-report instruments such as the Illness Perception Questionnaire-Revised (Moss-Morris et al., 2002) or its short form, the Brief Illness Perception Questionnaire (Broadbent et al., 2006), were used. On the latter, individual items represent subscales assessing each illness perception dimension.

In general, illness perceptions are consistently linked to psychological and physical outcomes in diseases such as diabetes, chronic fatigue syndrome, and HIV (Hagger & Orbell, 2006). They have been tested as predictors of stress, emotional responses, and physical responses (Trovato et al., 2012; Israel, White, & Gervino, 2015; Grayson et al., 2013). Studies of the illness perceptions of cancer patients are accumulating. Cook and colleagues (2015) identified illness perception dimensions that predicted post-traumatic stress and depressive symptoms in breast and prostate cancer patients (N=229). Specifically, timeline, identity, consequences, and attributing psychological causes for the illness predicted both stress and depressive symptoms, with treatment control and coherence also accounting for a significant proportion of the variance in stress. Additional studies have linked dimensions of emotional representation, consequences, control, identity, and timeline to depressive symptoms (Gray et al., 2015; McCorry et al., 2013; Silva, Moreira, & Canavarro, 2012; Dempster et al., 2011). Finally, despite the common occurrence of cancerrelated fatigue, we were able to locate only one study documenting its relation to illness perceptions. Pertl and colleagues (2012) found moderate to strong correlations between multiple illness perception dimensions and fatigue severity, with identity, consequences, and emotional representation being the highest.

The cancer studies above have been with patients with solid tumors with none, to the authors' knowledge, focusing on patients with blood cancers. This gap is noteworthy

considering differences in the diagnosis, course, and treatment of leukemias compared to solid tissue malignancies. For example, the majority (70–80%) of patients with chronic lymphocytic leukemia (CLL) are asymptomatic or only mildly symptomatic at diagnosis (Shanafelt et al., 2009). Further, treatment of early stage disease does not benefit survival. Thus, many patients undergo active surveillance where the disease is monitored and only treated once progression occurs. When initiated, treatment of CLL also differs from that observed in solid tumour patients. As CLL is incurable, the goal of treatment is to induce a remission of symptoms. Relapse is inevitable, however, and as patients with relapsed/ refractory disease pursue subsequent therapies, treatment options typically achieve shorter remissions (Burger et al., 2014). Differences in the diagnosis, course, and treatment of CLL raise the question of generalizability of illness perception findings from other disease sites.

The current study addresses limitations of the existing literature by examining how illness perceptions relate to common cancer sequelae – stress, depressive symptoms, and fatigue – in patients with relapsed/refractory CLL. We anticipated that, in general, a more negative perception of CLL would relate to more negative outcomes, as has been found in other illnesses (Hagger & Orbell, 2006). Of greater relevance, however, is which illness perceptions are related to what outcomes, particularly so because CLL illness perceptions have not been studied. Based on prior CLL research and clinical familiarity with patients, we expected patients to endorse more consequences, a higher influence of CLL on their emotions (emotional representation), a stronger illness identity, more illness concern, and a more chronic illness timeline. However, due to being incurable and chronic, we anticipated high endorsements of knowledge (coherence) about CLL, but low ability to control it (personal control and treatment control).

Method

Participants

Patients (N=147) with relapsed/refractory CLL participated. They were, on average, 64 years old (range=26–91), predominantly male (71%), and Caucasian (97%). Eighty-five percent of patients had a significant other, and the majority (78%) had received at least some college education. On average each patient had received 3 or more prior therapies (median=3, range=1–16), and 31% had at least one additional medical comorbidity as assessed with the Charlson Comorbidity Index (Charlson, Pompei, Ales, & MacKenzie, 1987).

Procedure

The Institutional Review Board of a university affiliated, National Cancer Institute designated comprehensive cancer center granted ethical approval for a phase II clinical trial of targeted therapy (Ibrutinib). Trial eligibility included individuals previously diagnosed and treated for CLL with a current indication for treatment, failure of at least one prior therapy, a life expectancy of greater than 2 months, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and ability to provide informed consent. Additional medical criteria were required to receive the investigational medication (e.g., normal organ function, previous receipt of ofatumumab, cytogenetic analyses by FISH). These data were a

part of the enrollment procedures, obtained as patients entered the trial with the self-report questionnaires being provided by a protocol nurse and patients completing them during the pre-treatment clinic appointment. Electronic medical records were used to obtain treatment history and illness comorbidity information.

Measures

Independent Variables

Illness perceptions: The Brief Illness Perception Questionnaire (BIPQ; Broadbent et al., 2006) is a self-report measure used to assess cognitive and emotional representations of illness. The BIPQ contains eight dimensional items, each with a 0–10 point scale. Higher scores on each item reflect stronger endorsement of the construct. Dimensions of illness perceptions assessed include consequences ("How much does your illness affect your life?"), emotional representation of illness ("How much does your illness affect you emotionally?"), identity ("How much do you experience symptoms from your illness?"), concern ("How concerned are you about your illness?"), personal control ("How much do you think your treatment can help your illness?"), coherence ("How well do you feel you understand your illness?"), and timeline ("How long do you think your illness will continue?"). Six-week test-retest reliability for the items ranges from .42 to .75. Concurrent validity with relevant measures, discriminant validity across illnesses, and predictive validity in different disease groups has been reported (Broadbent et al., 2006).

Outcomes

Cancer-specific stress: The Impact of Events Scale-Revised (IES-R; Horowitz, Wilner, & Alvarez, 1979; Weiss & Marmar, 1997) is a 22-item self-report questionnaire assessing traumatic reactions to cancer diagnosis and treatment. Factor analytic studies indicate that the measure examines three factors: intrusive thoughts (e.g., "I had dreams about being a cancer patient"), avoidant behaviors/thoughts (e.g., "I tried not to talk about it"), and hyperarousal (e.g., "I was jumpy and easily startled"). The current study used a sum of the intrusive thoughts and avoidant behaviors/thoughts scales. Participants rate the frequency of these feelings or events in the past week, using a five-point Likert scale ranging from 0 = not at all to 4 = extremely. Items are summed for a total score that can range from 0 to 64. The alpha reliability for this sample was 0.88, which is consistent with other studies reporting reliabilities of 0.78 to 0.83 (Horowitz et al., 1979; Weiss & Marmar, 1997).

Depressive symptoms: The Beck Depression Inventory-2nd edition (BDI-II; Beck, Steer, & Brown, 1996) is a 21-item self-report instrument assessing the severity of depressive symptoms. Patients are asked to rate how frequently they have experienced certain symptoms of depression (e.g., sadness, pessimism, loss of pleasure) during the past month on a scale from 0 to 3. Items are summed, with higher scores indicating more depressive symptoms. A cognitive-affective subscale score can be computed which excludes physical symptoms of depression (e.g., fatigue, insomnia). As somatic symptoms of depression may be confounded with physical symptoms commonly experienced by cancer patients, analyses were conducted using only the cognitive-affective subscale, as is recommended (Ritterband

& Spielberger, 2001). Scores on this subscale can range from 0 to 42. The alpha reliability coefficient for this sample is 0.86, which is consistent with the previously reported range of 0.86 to 0.93 (Beck et al., 1996).

Fatigue: The Fatigue Symptom Inventory (FSI; Hann et al., 1998) is an 11-item self-report questionnaire used to measure the frequency, severity, and daily pattern of fatigue, as well as its impact on quality of life in the past week. The Total Disruption Index (TDI), a 7-item subset of the FSI, was used. The TDI measures the degree of interference of fatigue on various aspects of life in the past week (e.g., enjoyment of life, work, relationships? with other people). Items are rated on an 11-point Likert scale from 0 = no interference to 10 = extreme interference. Total scores can range from 0 to 70, with higher scores indicating greater fatigue interference. The alpha reliability was 0.95, consistent with internal consistency values reported by Hann and colleagues (1998).

Data analysis

Data were analyzed using IBM SPSS 20.0 for Windows. Descriptive statistics summarized illness perceptions, outcome variables, and patient sociodemographic, and treatment characteristics. Control variables for regression analyses were selected on the basis of a significant correlation with any outcome variable. To maintain consistency in interpretability across regression models, any control variable correlated with an outcome would be used as a covariate in all regression analyses. Candidate control variables were sociodemographic (i.e., age, gender, marital status, education level, income) and disease/treatment (i.e., number of prior therapies and Charlson Comorbidity Index score).

Hierarchical multiple regression was used. Each illness perception item (8) was tested individually as a predictor of each outcome. This enables identification of associations between illness perception dimensions and outcomes that would be obfuscated by simultaneous inclusion of the items for all dimensions. Control variable(s) entry was the first step followed by the illness perception. General assumptions of linear regression including multicolinearity, variance of errors (homoscedasticity vs. heteroscedasticity), and normality of the error distributions were examined. To adjust for positive skew, all dependent variables were log transformed using log(x + 1). A Bonferonni adjusted alpha p < .002 (.05/24) was used.

Results

Descriptive and Preliminary

Descriptive data on illness perception and outcome variables are displayed in Table 1. Consistent with theory, there was variability in each illness perception dimension across the sample, with patients on average endorsing a strong understanding of CLL (M = 8.34, SD = 1.85), a high degree of treatment control (M = 8.14, SD = 1.87), and high levels of concern for their illness (M = 8.34, SD = 2.91). Patients perceived a moderate amount of consequences (M = 4.89, SD = 2.94) and a moderate illness identity (M = 4.41, SD = 2.85), and low levels of personal control (M = 3.56, SD = 2.78) and emotional representation (M = 3.68, SD = 2.89).

Results of candidate control selection revealed a negative correlation between number of prior therapies and cancer-specific stress (r = -.25, p < .01), such that higher numbers of previous treatment cycles were associated with lower levels of stress. For consistency, number of prior therapies was included as a covariate in the analyses for all outcomes.

Primary Analyses

Results are displayed in Table 2. Adjusted R^2 and standardized regression coefficients (β) are provided.

Consequences—Consequences was significantly related to all outcomes (*p*s <.001). All relationships observed were in the hypothesized direction, with perception of more negative consequences of CLL being related to higher levels cancer-specific stress (β = .373), depressive symptoms (β = .479), and fatigue (β = .504). R^2 values for the final models ranged from .167 (cancer-specific stress) to .244 (fatigue).

Emotional Representation—The perceived impact of CLL on one's emotional state was also related to all outcomes in the expected direction (*p*s <.001), with stronger perceived impact of CLL on emotions being related to higher levels of cancer-specific stress ($\beta = .$ 442), depressive symptoms ($\beta = .554$), and fatigue ($\beta = .419$). Final models accounted for 17.4% to 29.7% of the variance in the outcome measures.

Identity—Endorsement of more symptoms of CLL (identity) was significantly associated with fatigue ($\beta = .580$) such that higher values on the identity item were associated with higher levels of interference from fatigue, accounting for 33.4% of the variance in fatigue. The relation of illness identity to cancer-specific stress ($\beta = .191$) and depressive symptoms ($\beta = .249$) was not significant.

Illness Concern—Illness concern was only related to cancer-specific stress ($\beta = .300$), such that more concern about one's CLL was related to higher levels of cancer-specific stress. The variance accounted for was 12.5%.

Personal Control, Treatment Control, Coherence, and Timeline—Personal control, treatment control, coherence, and timeline were unrelated to all outcomes of interest.

Other Analyses

For the interest of the reader, multivariate regression analyses testing all illness perception dimensions simultaneously were conducted. Models entered number of previous therapies in the first step followed by the 8 illness perception dimensions in the second step to predict cancer-specific stress, depressive symptoms, and fatigue.

Illness perceptions accounted for 25% of the variance in cancer-specific stress ($R^2 = .26, p < .01$). Fewer prior CLL therapies ($\beta = -.247$), more perceived consequences ($\beta = .276$), higher values on emotional representation ($\beta = .201$), and more concern for one's illness ($\beta = .187$) predicted stress. Illness perceptions accounted for 36% of the variance in depressive symptoms ($R^2 = .40, p < .01$). More perceived consequences ($\beta = .315$), higher values on

emotional representation ($\beta = .390$) and personal control ($\beta = -.181$) predicted depressive symptoms. Illness perceptions accounted for 43% of the variance in fatigue ($R^2 = .46, p < .01$). Stronger illness identity ($\beta = .482$) and illness concern ($\beta = -.177$) predicted fatigue.

Discussion

Chronic lymphocytic leukemia is phenomenologically distinct from most cancers, yet understudied. This study is the first to examine illness perceptions as predictors of stress, depression, or fatigue in an adult blood cancer, and provides new psychosocial data on CLL patients with relapsed/refractory disease. Within this context, we have demonstrated that different illness perception dimensions were related to different psychological responses. In addition, perceived consequences and emotional representation were notable as they covaried with all outcomes.

Interestingly, patients with relapsed/refractory CLL endorsed certain illness perception dimensions in ways contrary to findings from previous research. For example, scores on emotional representation were low (M = 3.68, SD = 2.89), which is a departure from higher scores reported in other cancer samples (Llewellyn, McGurk, & Weinman, 2007; Rozema et al., 2009). Similarly, beliefs in treatment's ability to control the illness were high (M = 8.14,SD = 1.87) despite CLL being incurable. These findings may be understood in the context of the treatment experiences of those having CLL. Although relapse is inevitable, treatment regimens, particularly front line options, are typically effective in inducing temporary remissions (Byrd et al., 2014). Thus, it could be that patients with multiple relapses have, over time, developed stronger beliefs in the ability of treatment to control the disease, at least for some period of time. Also, these patients were entering a phase II trial with a novel targeted therapy (Ibrutinib) with encouraging clinical data (Byrd et al., 2013) for clinical efficacy. Their CLL history, as well as high treatment control beliefs, may be responsible for the reports of low emotional impact of the disease. Future studies of patients with other CLL treatment histories such as those on active surveillance and those initiating a first treatment may help clarify the importance of treatment history in illness perceptions.

It was also noteworthy that a higher number of prior treatments covaried with lower cancerspecific stress. This finding may be consistent with an effect observed in breast cancer patients with recurrence. In their examination of psychological responses to recurrent breast cancer, Andersen and colleagues (2005) observed that patients (N=30) followed from initial diagnosis through recurrence reported equivalent stress at both time points. However, whereas stress at initial diagnosis was associated with emotional distress and reduced quality of life, stress at recurrence was not accompanied by these responses. The latter results were conceptualized from a learning perspective, namely, previous experiences with cancer enhanced emotional resilience to later experiences. Though not identical to CLL, recurrent breast cancer is similar in regards to a return of symptoms that have been absent for some period of time. It could be that a number of factors--previous experience with cancer treatments and their side effects, acquaintance with the medical system, knowledge of monetary obligations, and existing social support structures, and others--may contribute to diminished stress as the number of CLL treatment cycles increase.

However, beyond the contribution of prior therapies, illness perception dimensions of consequences, emotional representation, and illness concern were related to cancer-specific stress. These findings are consistent with those of Cook and colleagues (2015) who observed significant relationships between illness perceptions and post-traumatic stress in breast and prostate cancer patients. This conceptual replication has theoretical implications. For example, the average number of previous treatments received by these patients was 3.54 (range = 2–16), with 20% relapsing 5 or more times previously. Despite this, it was patients' subjective perception of their illness that accounted for the majority of variance in cancer-specific stress. This finding validates the Self-Regulatory Model, and expands the literature on the relevance of illness perceptions to psychological outcomes for people with chronic illness.

These data also add knowledge to our understanding of the relationship between illness perceptions and depressive symptoms. Consistent with hypotheses, emotional representation and consequences were positively associated with depressive symptoms, accounting for 29.7% and 20.7% of the variance, respectively. Contrary to previous studies (Gray et al., 2014; Price et al., 2011; Dempster et al., 2011), our data did not support a relationship between control beliefs and depressive symptoms. This finding is noteworthy, as control beliefs have been traditionally described as influential for one's emotional response to a health threat (Lau & Hartman, 1983; Diefenback & Leventhal, 1996). That is, negative emotional responses such as depressed mood are more likely among those who appraise their situation as uncontrollable. The incurable nature of CLL could have made control beliefs less relevant to depressive symptoms, though this has not been the case in other incurable conditions such as multiple sclerosis (Jopson & Moss-Morris, 2003).

Results also support the relevance of illness perceptions to the experience of fatigue. Interference from CLL-specific fatigue was highest among those who reported more consequences, more impact of CLL on their emotions, and endorsed a stronger illness identity. Interestingly, the final model containing the identity dimension accounted for 33.4% of the variance in fatigue, compared to only 7.2% and 4.8% of variance in cancer-specific stress and depressive symptoms. These values indicate that illness identity is more strongly related to physical functioning than psychological in this sample, an effect that can be observed in the R² values of previous studies (Moss-Morris, Petrie, & Weinman, 1996; Borge, Moum, Puline Lein, Austegard, & Wahl, 2014). As initially conceptualized, illness identity is the label a lay person applies to a set of symptoms and the type and number of symptoms that an individual attributes to the illness (Broadbent et al., 2006). Thus, it is expected that individuals who perceive their illness as causing more symptoms go on to report greater interference from fatigue.

The findings have clinical implications. Based on the consistent relationships of perceived consequences to outcomes, modification of beliefs about the consequences of CLL, or utilization of problem-solving or other strategies to reduce perceived consequences of the disease might be beneficial. Interventions focused on restructuring maladaptive illness perceptions have been efficacious in improving outcomes for others, such as those with lower back pain (Siemonsma et al., 2013) or non-cardiac chest pain (Jonsbu, Martinsen, Morken, Moum, & Dammen, 2013). Emotional representation, too, was related to all

outcomes. As such, interventions aimed at reducing negative emotional responses to the disease may benefit not only psychological outcomes, but fatigue as well. Finally, our findings indicate patients with fewer previous therapies (or no prior therapy) may be more susceptible to stress, suggesting that stress management interventions may best serve those entering treatment for the first time.

The methods and context for the study require mention. Although illness perceptions are conceptualized as precursors (Leventhal et al., 1980), the cross sectional design used here prevents inferences about the temporal relationship among variables. Future studies examining trajectories of illness perceptions and their covariation with common cancer sequelae are needed. Relatedly, with simultaneous assessment of illness perceptions and outcomes we considered the possibility of conceptual overlap, for example, that between emotional representation and depressive symptoms. Inspection of intercorrelations (See Table 1) suggests that shared variance between such variables was less than 34%. Of more interest, however, are the novel findings relating illness perceptions to conceptually distinct outcomes (e.g., emotional representation with fatigue, consequences with cancer-specific stress). The sample participating was homogenous, with the majority of individuals being Caucasian and educated. The mean age of patients was 64 years, which, although similar to that observed in CLL clinical trials (e.g., Else et al., 2008; van den Broek et al., 2015), is lower than the median age of CLL diagnosis (71 years; Howlader et al., 2015) recorded in national samples.

In summary, chronic lymphocytic leukemia is an understudied population with an atypical course and treatment trajectory. In this context, our study sought to examine the relation of illness perceptions to common sequelae of the cancer experience. Results demonstrated that an individual's perception of CLL is associated with cancer-specific stress, depressive symptoms, and fatigue above and beyond the influence of previous treatments received. Further research is needed, particularly among those with relapsed/refractory disease, to garner a better understanding of the role that illness perceptions serve in the development and progression of psychological and physical responses to the disease.

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Table 1

Summary statistics and correlations for outcome, illness perception, treatment, and demographic variables (N=147).

Variable	Mean (SD)	Observed Range	Bivaria	Bivariate Correlations	lations
Outcome			1.	2.	3.
1. Cancer-Specific Stress (IES)	9.76 (8.06)	0-33.43		.52**	.30 **
2. Depressive Symptoms (BDI-II)	2.83 (3.43)	0-16.00			.54 **
3. Fatigue Interference (FSI)	16.47 (17.32)	0-70.00			
Illness Perception Dimension					
Consequences	4.89 (2.94)	0-10	.31 **	.45 **	.56**
Emotional Representation	3.68 (2.89)	0-10	.48	.58**	.46**
Identity	4.41 (2.84)	0-10	.18*	.21*	.58**
Concern	7.29 (2.91)	0-10	.32 **	.20*	60.
Personal Control	3.56 (2.78)	0-10	10	19*	08
Treatment Control	8.14 (1.87)	0 - 10	07	16	02
Coherence	8.34 (1.85)	0-10	04	10	01
Timeline	7.45 (2.77)	0-10	16	08	.01
Treatment and Demographic					
Number of prior therapies	3.55 (2.66)	1–16	20^{*}	00	60.
Age (years)	64.06 (10.75)	26–91	07	07	60:

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** Correlation is significant at the 0.01 level (2-tailed). Table 2

Regression model summary: Illness perceptions predicting stress, depressive symptoms, and fatigue (N=147).

Cancer-Specific Stress (IES-R) Depressive Symptoms (BDI-II) Fatigue (FSI)

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	•				0	(mar) and in a
	R^2	β	R^2	β	R^2	β
Model 1	.039		007		.007	
Model 2	.167		.207		.244	
Prior therapies		292		135		.008
Consequences		.373 ***		.479 ***		.504 ***
Model 1	.045		007		.004	
Model 2	.235		.297		.174	
Prior therapies		201 **		003		.122
Emotional		.442		.554 ***		.419
Representation						
Model 1	042		007		.004	
Model 2	.072		.048		.334	
Prior therapies		240^{**}		051		.041
Identity		.191 *		.249 **		.580 ***
Model 1	.041		007		.004	
Model 2	.125		.014		004	
Prior therapies		201 *		017		.104
Concern		.300***		.168		.006
Model 1	.040		007		.006	
Model 2	.044		.050		001	
Prior therapies		226		043		.116
Personal Control		107		254 **		.014
Model 1	.042		007		.004	
Model 2	.036		.015		000.	

	Cancer-Specil	Cancer-Specific Stress (IES-R)		Depressive Symptoms (BDI-II)	Fatigı	Fatigue (FSI)
	R^2	β	R^{2}	β	R^2	β
Prior therapies		225 **		037		.103
Treatment Control		026		171 *		057
Model 1	.042		007		.004	
Model 2:	.042		002		.003	
Prior therapies		226 **		026		.105
Coherence		083		110		076
Model 1	.044		006		001	
Model 2	090.		002		007	
Prior therapies		230 **		044		.080
Timeline		152		109		044
*** p <.002;						
** p <.01;						
* p <.05						

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