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Pre-treatment Symptom Cluster in Breast Cancer Patients is Associated with Worse Sleep, Fatigue and Depression during Chemotherapy

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Abstract

Objective—The concept of symptom clusters is relatively new in cancer patients' symptom management. This study, which spanned four cycles of chemotherapy, combined three commonly seen pre-treatment symptoms in cancer patients (i.e., sleep disturbances, fatigue and depression) into one symptom cluster, to explore the associations between pre-treatment cluster categories and longitudinal profiles of these same symptoms during chemotherapy.

Methods—This was a prospective study. Seventy-six women with newly diagnosed stage I–III breast cancer, scheduled to receive at least four cycles of adjuvant or neoadjuvant anthracycline-based chemotherapy participated. Data were collected at seven time points before and during treatment. Sleep quality was measured with the Pittsburgh Sleep Quality Index (PSQI). Fatigue was measured with the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF). Depressive symptoms were measured with the Center of Epidemiological Studies-Depression (CES-D). Patients were divided into three groups based on the number of symptoms they experienced before the start of chemotherapy (i.e., no symptoms, 1–2 symptoms or all three symptoms) and a symptom cluster index (SCI) was computed.

Results—All women reported worse sleep, more fatigue and more depressive symptoms during treatment compared to baseline (all p's <0.01); however, those women with a higher symptom cluster index (i.e., more symptoms pre-treatment) continued to experience worse symptoms during treatment compared to those who began with fewer symptoms (all p's <0.01).

Conclusions—A higher clinically relevant-based pre-treatment symptom cluster was associated with more sleep disturbances, greater fatigue and more depressive symptoms during chemotherapy. Specific interventions for these pre-treatment symptoms may improve the frequency and severity of

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these same symptoms during chemotherapy, when they are most severe and most disruptive to quality of life.

Keywords

breast cancer; symptom cluster; sleep disturbances; fatigue; depression

Background

Sleep disturbances, fatigue, and depression are all common in patients with cancer [1]. As these cancer-related symptoms are highly correlated with each other [2,3,4,5,6,1], the term "symptom cluster" has been introduced. Symptom clusters, first reported by Dodd and colleagues, were defined as three or more concurrent and related symptoms frequently found in cancer patients [7,8,9]. In a review, Miaskowski et al.[10] remarked that the majority of clinical studies on cancer-related symptoms focused on one symptom and suggested studies focusing on evaluating multiple symptoms, i.e., symptom clusters, using longitudinal study design. Miller et al. reviewed cancer-related symptoms, such as depression, fatigue, sleep disturbances and cognitive dysfunction, and concluded that they may share the same neuroendocrine-immune pathophysiologic mechanisms. The authors suggested that behavioral status should be assessed in all cancer patients throughout their disease encounter [11].

Studies have shown that interventions may improve multiple symptoms at the same time [12, 13,14], suggesting that the symptoms may share some common mechanisms [15,5,10]. Particular biomarkers, such as serum cortisol, melatonin, and serotonin are all associated with fatigue, sleep and depressive symptoms during chemotherapy [5]. It has been suggested that some cancer-related symptoms (e.g., sleep disturbance, fatigue, and affective symptoms) may also share common cytokine-based neuroimmunologic mechanisms [16,15,17,18,19,11]. This evidence thus suggests that there are both clinical as well as physiological reasons to cluster symptoms. Combining symptoms into a symptom cluster therefore, should be based on both clinical relevance as well as physiological or neurochemical pathways.

Barsevick et al. [1], in a recent review, suggested that new studies needed to consider critical issues such as longitudinal design and new models and innovative statistical approaches for the identification and analysis of symptom clusters. This study attempted to address some of these issues by focusing on multiple symptoms followed over the course of four cycles of chemotherapy, using a standard likelihood theory for mixed-effect models.

We previously reported that sleep disturbance, fatigue and depressive symptoms were reported by cancer patients before the initiation of chemotherapy, and that these symptoms were significantly correlated with each other [3], these clinically relevant symptoms were chosen to form the symptom cluster. The associations between this symptom cluster and the severity of these same symptoms during chemotherapy were then explored. We hypothesized that those women who began treatment with a higher symptom cluster index (i.e., more symptoms) would also suffer from more symptoms during treatment than those women who began treatment with a lower symptom cluster index.

Patients and Methods

Patients

Ninety-five women with breast cancer were enrolled (see Figure 1). Of the 95 patients, 76 women had complete subjective and objective baseline data on sleep quality, fatigue and mood. The mean age of the 76 patients was 51.1 years (SD=9.1, range 34–79 years). All women were newly diagnosed with stage I–III breast cancer (33% with stage I, 49% with stage II, 18% with

stage III) and had not previously received chemotherapy. All participants were scheduled to receive at least 4 cycles of adjuvant or neoadjuvant anthracycline-based chemotherapy with each cycle three weeks apart (95% with doxorubicin and cyclophosphamide [AC], or AC plus fluorouracil, AC plus docetaxel, or AC plus paclitaxel; 5% with cyclophosphamide, epirubicin and fluorouracil [CEF]). Of the 76 women, 72% were Caucasian, 68% were married, 75% had at least some college, and 74% reported an annual income of more than $30,000. Pregnant women, those undergoing bone marrow transplants, and those with metastatic (including inflammatory) breast cancer, with confounding underlying medical illnesses, with significant pre-existing anemia or with other physical or psychological impairments were excluded.

The study was approved by the University of California at San Diego (UCSD) Committee on Protection of Human Subjects and by the Rebecca and John Moores UCSD Cancer Center's Protocol Review and Monitoring Committee.

Measures

Sleep quality

Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI) [20]. The PSQI is a 19-item questionnaire which rates patients' reports of sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction. The total PSQI scores range from 0–21 with high scores reflecting poor sleep quality. A total score above 5 is generally considered poor sleep. Although studies suggested that a cut-off score of 8 may be more appropriate to indicate poor sleep in clinical populations [21,22], a cut-off of 5 is the generally utilized score in the insomnia literature and was used in this study.

Fatigue

Fatigue was assessed with the 30-item Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF), which has been shown to be a valid and reliable tool for the multidimensional assessment of cancer-related fatigue for both clinical and research applications [23,24]. The items of the MFSI-SF collapse into five subscales of fatigue-dimensions: General, Emotional, Physical, Mental, and Vigor. Each subscale includes 6 items and each item is rated on a 5-point scale indicating how true the statement was during the last week (0=not at all, 4=extremely). Higher scores indicate more severe fatigue, except for the Vigor subscale, where a higher score indicates less fatigue (more Vigor). The sum of General, Physical, Emotional, and Mental subscale scores minus the Vigor subscale score generates a total fatigue score. The range of possible scores for each subscale is 0 to 24, and the range for total fatigue score is −24 to 96. While the MFSI-SF does not report cut-off scores for defining fatigue, a study by Stein et al. [23] reported that in adults with no cancer, the mean total MFSI-SF score was 0.85.

Mood

Depressive symptoms were assessed with the Center of Epidemiological Studies-Depression (CES-D) scale [25]. The CES-D is a 20-item scale of depressive symptoms. Since the CES-D reflects cognitive and affective symptoms rather than somatic symptoms of depression, it is highly recommended for use with patients with medical problems. The range of scores of the CES-D is 0–60 with higher scores representing more symptoms of depression. An arbitrary cut-off score for depressive symptoms has been set at 16 [25]. DSM-IV [26] depression data were not collected.

Procedure

Detailed procedural information can be found in Liu et al [27]. Briefly, after consent forms were signed, medical records were abstracted for medical history and current medication use. Data were collected at the following seven time points: before the start of the first cycle of chemotherapy (baseline or pre-treatment), during each week of the three weeks of cycle 1 (week 1 [C1W1]: chemotherapy administration; week 2 [C1W2]: point of nadir of blood count; week 3 [C1W3]: recovery), and during each week of the three weeks of cycle 4 (C4W1, C4W2 and C4W3). In general, baseline data collection began the week before chemotherapy, followed by data collection on the morning following chemotherapy administration (week 1). Data collected in each subsequent week (weeks 2 and 3) were collected on the same day of the week as during week 1. All questionnaires were completed once at each of the same seven time points.

A symptom cluster index (SCI) was computed for each woman, based on both the severity and prevalence of baseline scores on the PSQI, MFSI-SF *and* CES-D. Three groups were formed for purposes of analyses. The SCI 0 group (n=15) consisted of women whose scores on the sleep quality, fatigue and mood scales where within normal limits, i.e., no symptoms based on PSQI≤5, MFSI≤0.85 *and* CES-D≤16 [20,23,25]. The SCI 1–2 group (n=43) consisted of women who scored above the cut-off on one or two of the three scales, i.e., severe symptoms on 1–2 symptoms based on PSQI>5, MSFI>0.85 *or* CED-D>16. The SCI 3 group (n=18) consisted of women who scored above the cut-off on all three scales, i.e., severe symptoms on all 3 based on PSQI>5, MSFI>0.85 *and* CED-D>16.

Data analysis

Group differences in demographic and background characteristics were assessed with analysis of variance (ANOVA) and chi-square tests. Pearson correlation analyses were performed among the total scores of the three questionnaires at baseline. Differences in sleep quality, fatigue and depressive symptoms in the three groups over time (group × time interaction) were assessed with repeated-measures analysis of variance (based on standard likelihood theory for mixed-effect models), with visits as the within-subjects factor (time effect) and group as the between-subjects factor (group effect).

All analyses were performed using version 9.1 of SAS (SAS Institute Inc 2003). All statistical tests with p-values <0.05 are reported as statistically significant.

Results

At baseline (pre-treatment), there were no significant differences in age, ethnicity, education, income, tumor stage, chemotherapy regimen, marital or menopausal status among the three groups (see Table 1).

Symptoms before chemotherapy

Fifty (66%) of the 76 women reported poor sleep quality (PSQI score >5), 48 (63%) reported fatigue (MFSI-SF score >0.85), and 19 (25%) reported depressive symptoms (CES-D score >16). These symptoms were significantly correlated with each other (see Table 2).

Sleep Quality

Total PSQI scores by group for the seven time points are shown in Figure 2. Mixed-effect models revealed an overall group effect (p<0.0001) and an overall time effect (p=0.026), but no group × time interaction. The significant group effect suggests that those women with a higher index had worse sleep than those with a lower index. At baseline, the PSQI scores for

SCI 1–2 and SCI 3 groups were significantly higher, suggesting worse sleep, than PSQI scores for the SCI 0 group (both $p<0.0001$). This pattern was consistent throughout treatment with the SCI 0 group continuing to have the lowest total PSQI scores and the SCI 3 group having the highest. The significant time effect suggests that there were changes in sleep over time. During treatment, PSQI scores for the SCI 0 group significantly increased from baseline to C4W1 ($p=0.006$). The fact that there was no group × time interaction suggests that the baseline group differences were maintained during treatment with the SCI 3 group continuing to report worse sleep than the other two groups and the SCI 1–2 group reporting worse sleep than the SCI 0 group.

Fatigue

Total MFSI-SF scores by group are shown in Figure 3. Mixed-effect models revealed an overall group effect ($p<0.0001$) and an overall time effect ($p<0.0001$), but no group × time interaction ($p=0.10$). The significant group effect suggests that those women with a higher index had more fatigue than those with a lower index. At baseline, the MFSI-SF scores for SCI 1–2 and SCI 3 groups were significantly higher, suggesting more fatigue, than MFSI-SF scores for the SCI 0 group (both $p<0.01$). This pattern was consistent throughout treatment with the SCI 0 group continuing to have the lowest total MFSI-SF scores and the SCI 3 group having the highest. The significant time effect suggests that there were changes in fatigue over time. During treatment, MFSI-SF scores for the SCI 0 group significantly increased from baseline to C1W1 ($p=0.001$), C4W1 ($p=0.011$), C4W2 ($p=0.002$), and C4W3 ($p=0.012$). The fact that there was no group × time interaction suggests that the baseline group differences were maintained during treatment with the SCI 3 group continuing to report more fatigue than the other two groups and the SCI 1–2 group reporting more fatigue than the SCI 0 group.

Mood

Total CES-D scores by group are shown in Figure 4. Mixed-effect models revealed an overall group effect ($p<0.0001$) and an overall time effect ($p<0.0001$) but no significant group × time interaction ($p=0.061$). The significant group effect suggests that those women with a higher index had more depressive symptoms than those with a lower index. At baseline, the CES-D scores for SCI 1–2 and SCI 3 groups were significantly higher, suggesting more depressive symptoms, than CES-D scores for the SCI 0 group (both $p<0.05$). This pattern was consistent throughout treatment with the SCI 0 group continuing to have the lowest total CES-D scores and the SCI 3 group having the highest. The significant time effect suggests that there were changes in depressive symptoms over time. During treatment, CES-D scores for the SCI 0 group significantly increased from baseline to C4W1 ($p=0.005$) and C4W2 ($p=0.014$). The fact that there was no group × time interaction suggests that the baseline group differences were maintained during treatment with the SCI 3 group continuing to report more depressive symptoms than the other two groups and the SCI 1–2 group reporting more depressive symptoms than the SCI 0 group.

Discussion

Breast cancer patients report a wide range of symptoms before the start of treatment, with over half reporting poor sleep and fatigue and a quarter reported depressive symptoms. In this study, the severity and prevalence of these symptoms was used to create a symptom cluster index and data, spanning four cycles of chemotherapy, were analyzed to examine the relationship between this index and the severity of symptoms during treatment. The results suggested that a higher pre-treatment symptom cluster index was associated with worse symptoms during chemotherapy. All women, regardless of the severity or frequency of their initial complaints, experienced worse sleep, more fatigue and more depressive symptoms during treatment compared to baseline. However, group differences seen at baseline remained with those women

with a higher symptom cluster index (i.e., more frequent and more severe symptoms pre-treatment) experiencing more severe symptoms during treatment compared to those who began with a lower index.

The concept of symptom clusters is relatively new in cancer patients' symptom management [10,1]. The 2002 NIH State-of-the-Science conference on symptom management in cancer concluded that too many cancer patients with depression and fatigue receive inadequate treatment for their symptoms [28]. This resulted in a call for prospective studies on the definition, occurrence, assessment and treatment of these symptoms, as well as for theoretically driven research to support the concept of cancer symptom clusters [28]. Based on this call for action and in response to the challenges set forth by Miaskowski et al.[10] and Barsevick et al. [1], this study used a longitudinal design and new statistical approaches to identify and analyze symptom clusters.

Other statistical approaches (such as cluster analysis, principal components) were considered but were not used. Although a cluster analysis would identify “clusters” of participants with similar symptoms, translating these “clusters” into the clinical setting would be difficult, i.e., assigning a future patient into a particular cluster might prove impossible since the clustering method would not provide a clear algorithm for classifying patients into clusters. The approach used in this study is intuitive and easy for the clinician to implement. In addition, it is justified by the high correlations between symptom scales. Finally, the models used to assess sleep, mood, and fatigue data during the cycles of chemotherapy used state-of-the-art statistical techniques based on mixed models, which are the method of choice for analyzing longitudinal unbalanced data.[29]

Some clinical studies have shown that particular interventions effective for one cancer-related symptom may also be effective for other symptoms [12,13,14]. Several studies of behavioral therapies for depression and insomnia have also resulted in improvements in anxiety, fatigue and quality of life [30,12,14,31]. The results of those studies in combination with the results of this study suggest that these symptoms indeed might best be considered as a cluster. Barsevick and colleagues suggested that intervention studies should focus on optimal management of all symptoms in a symptom cluster [1]. If specific interventions targeting a cluster of symptoms are begun before the initiation of chemotherapy, it is possible that patients will also experience fewer symptoms during treatment. Randomized controlled treatment studies exploring these questions are needed.

In conclusion, based on clinical relevance, we chose three, highly correlated symptoms frequently seen among breast cancer patients to form a symptom cluster. The symptom cluster index was then based on both frequency and severity of symptoms. The number of symptoms reaching a level of clinical severity (i.e., standardized cut-off levels for presence of that symptom) was used to determine if the symptom was present (ie., severity). The number of symptoms was used to compute the symptom cluster index, with a higher index reflecting the presence of more symptoms. The index therefore, represents both prevalence and severity. To our knowledge, this is the first study to report that breast cancer patients with a higher symptom cluster index pre-treatment also have more severe symptoms during treatment. Future studies are needed to examine symptom cluster treatment strategies.

Acknowledgments

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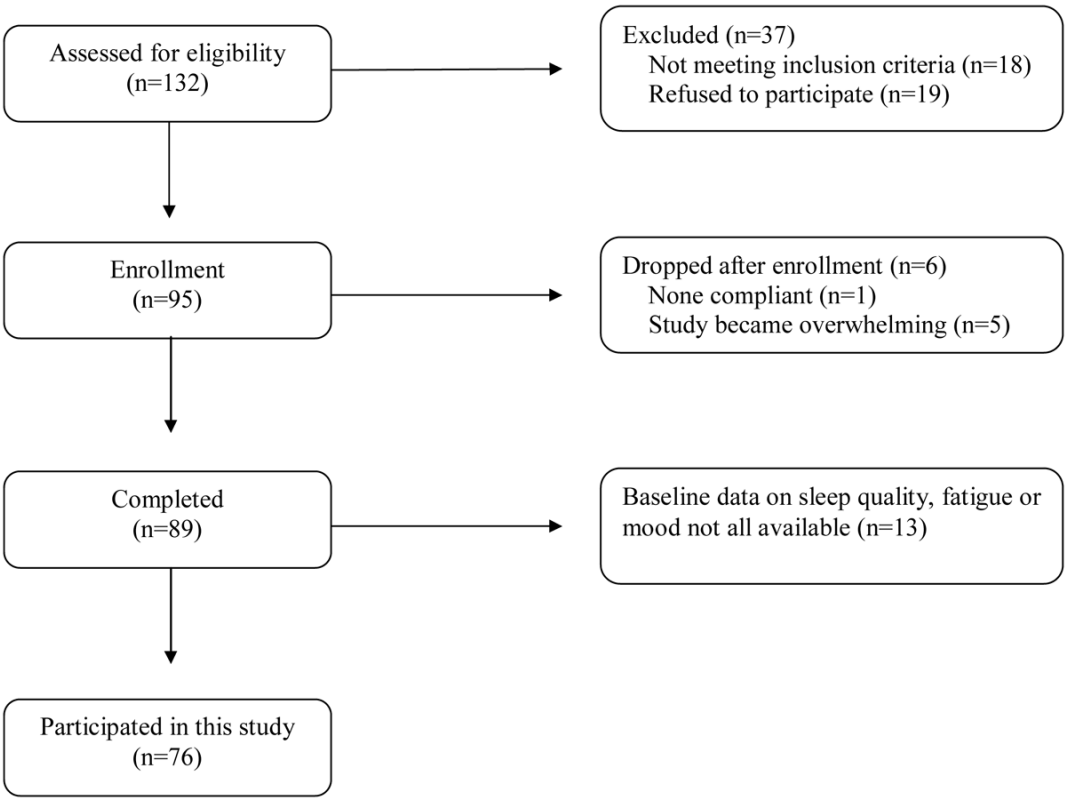

Figure 1. Screening and Enrollment Flowchart
CONSORT diagram showing the flow of participants

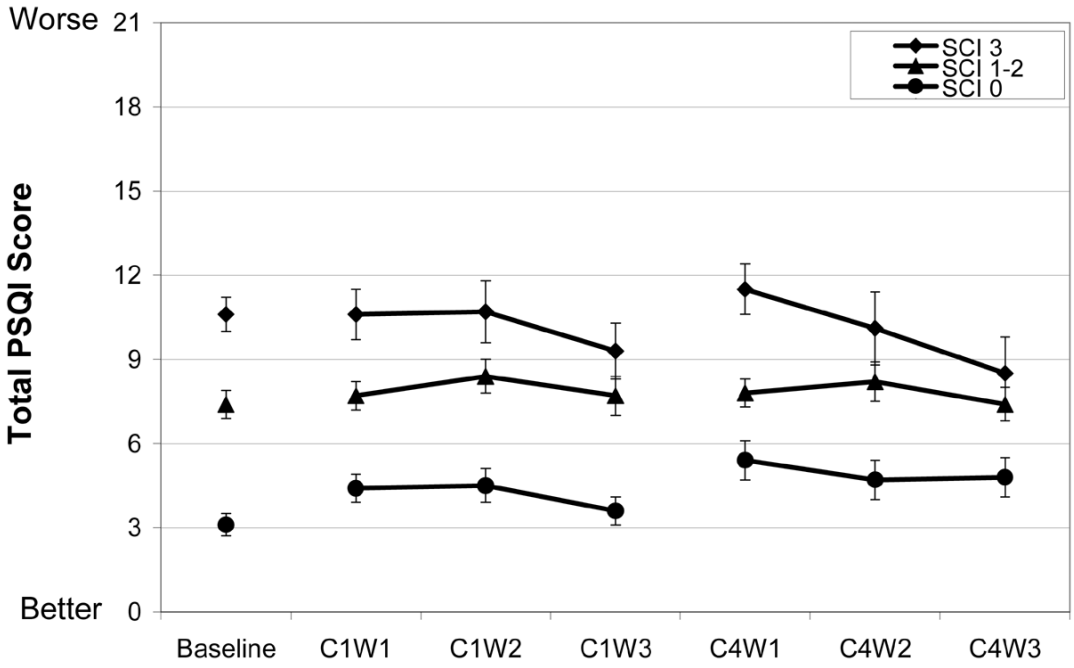

Figure 2. Total PSQI Score by Cycle/Week

Sleep quality as measured by the PSQI. All groups experienced worse sleep quality during treatment compared to pre-treatment (baseline) (overall group effect: $p<0.0001$; overall time effect: $p=0.026$). During treatment, the SCI 3 continued to report worse sleep than the other two groups, and the SCI 1–2 group continued to report worse sleep than the SCI 0 group (group by time interaction: $p= 0.13$).

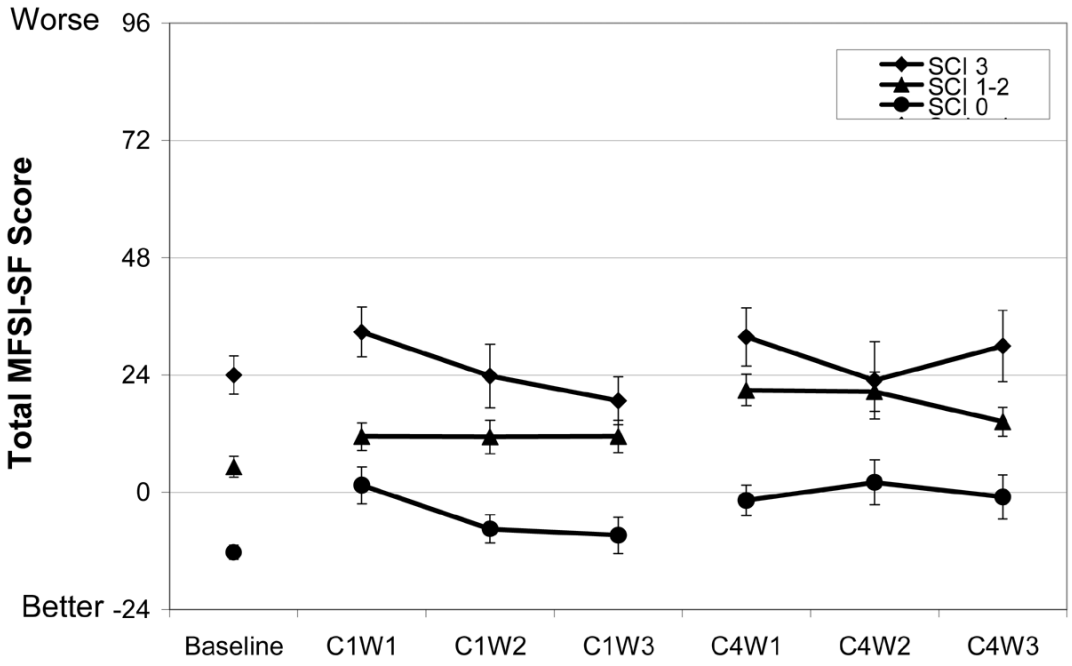

Figure 3. Total MFSI-SF Score by Cycle/Week

Fatigue as measured by the MFSI-SF. All groups experienced more fatigue during treatment compared to pre-treatment (baseline) (overall group effect: $p<0.0001$; overall time effect: $p<0.0001$). During treatment, the SCI 3 continued to report worse fatigue than the other two groups, and the SCI 1–2 group continued to report worse fatigue than the SCI 0 group (group by time interaction: $p= 0.10$).

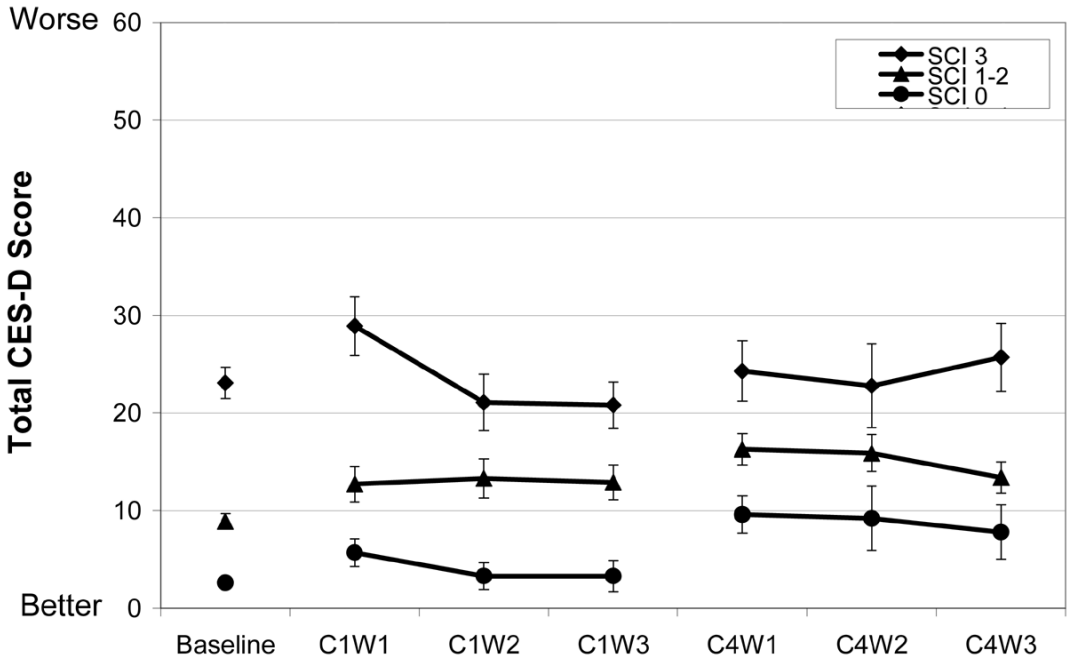

Figure 4. Total CES-D Score by Cycle/Week

Depressive symptoms as measured by the CES-D. All groups experienced more depressive symptoms during treatment compared to pre-treatment (baseline) (overall group effect: $p<0.0001$; overall time effect: $p<0.0001$). During treatment, the SCI 3 continued to report more depressive symptoms than the other two groups, and the SCI 1–2 group continued to report more depressive symptoms than the SCI 0 group (group by time interaction: $p= 0.06$).

Table 1

Demographic and Disease Characteristics of the Participants

Characteristics	Total (n=76)	SCI 0 Group (n=15)	SCI 1–2 Group (n=43)	SCI 3 Group (n=18)	p
Age (Mean ± SD)	51.1 ± 9.1	52.2 ± 8.6	51.6 ± 10.0	49.0 ± 9.8	0.56
Ethnicity [n (%)]					
Caucasian	55 (72.4)	11 (73.3)	33 (76.7)	11 (61.1)	0.46
Non-Caucasian	21 (27.6)	4 (26.7)	10 (23.3)	7 (38.9)	
Education [n (%)]					
Below high school	4 (5.3)	2 (13.3)	1 (2.3)	1 (5.6)	0.19
Completed high school	15 (19.7)	1 (6.7)	9 (20.9)	3 (27.8)	
Some college	20 (26.3)	6 (40.0)	8 (18.6)	6 (33.3)	
Completed college and above	37 (48.7)	6 (40.0)	25 (58.2)	6 (33.3)	
Marital status [n (%)]					
Never married	9 (11.8)	3 (20.0)	3 (7.0)	3 (16.6)	0.25
Divorced/separated/widowed	15 (19.8)	4 (26.7)	6 (14.0)	5 (27.8)	
Married	52 (68.4)	8 (53.3)	34 (79.0)	10 (55.6)	
Personal annual income [n (%)]					
≤ $30,000	11 (14.5)	3 (20.0)	5 (11.6)	3 (16.7)	0.68
> $30,000	56 (73.7)	11 (73.3)	31 (72.1)	14 (77.8)	
Refused to answer	9 (11.8)	1 (6.7)	7 (16.3)	1 (5.5)	
Menopausal status [n (%)]					
Pre-menopauses	30 (39.5)	5 (33.3)	15 (34.9)	10 (55.5)	0.65
Peri-menopause	12 (15.8)	3 (20.0)	7 (16.3)	2 (11.1)	
Post-menopause	20 (26.3)	3 (20.0)	14 (32.5)	3 (16.7)	
Hysterectomy	14 (18.4)	4 (26.7)	7 (16.3)	3 (16.7)	
Tumor stage [n (%)]					
Stage I	25 (32.9)	4 (26.7)	17 (39.5)	4 (22.2)	0.11

Characteristics	Total (n=76)	SCI 0 Group (n=15)	SCI 1–2 Group (n=43)	SCI 3 Group (n=18)	p
Stage II	37 (48.7)	5 (33.3)	21 (48.8)	11 (61.1)	
Stage III	14 (18.4)	6 (40.0)	5 (11.6)	3 (16.7)	
Chemotherapy regimen [n (%)]					
AC + fluorouracil/docetaxel/paclitaxel	72 (94.7)	15 (100.0)	40 (93.0)	17 (94.4)	0.58
CEF	4 (5.3)	0	3 (7.0)	1 (5.6)	

Note: SCI = Symptom Cluster Index

AC = doxorubicin and cyclophosphamide

CEF = cyclophosphamide, epirubicin and fluorouracil

Table 2

Correlation Coefficients among Sleep Disturbances, Fatigue and Depressive Symptoms at Baseline

	Total MFSI-SF score	**Total CES-D score**
Total PSQI score	0.4574 ($p<0.0001$)	0.5671 ($p<0.0001$)
Total MFSI-SF score		0.7136 ($p<0.0001$)