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Psychologic and Biologic Factors Associated with Fatigue in Patients with Persistent Radiculopathy

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Abstract

Fatigue is a common symptom associated with neuropathic pain (NP) and can have negative consequences on psychosocial functioning, physical endurance, and quality of life. Recent evidence indicates that immune activation modulated through the increased release of proinflammatory cytokines can predict fatigue in some patient populations. Although earlier studies have shown that immune activation is a pathophysiologic feature of NP, there have been no studies to examine the relationship between immune activation and fatigue in persons with NP. Therefore, the purpose of this exploratory study was to: 1) determine the relationships among fatigue, pain, psychosocial factors, and selected biologic markers of immune activation (interleukin [IL] 6 and soluble IL-6 receptor [sIL-6R]) in participants with persistent radiculopathy; and 2) determine the differences in these variables based on fatigue severity. Participants (n = 80) were classified according to their level of fatigue as low (27.5%), moderate (32.5%), or high (40%), and significant differences were found between fatigue categories (p =. 001). Multivariate analyses of variance revealed that individuals with moderate to high levels of fatigue differed from those with the lowest levels of fatigue in psychologic distress, depressive symptoms, IL-6, and sIL-6R, whereas the differences between moderate and high levels of fatigue were significant for psychologic distress and sIL-6R only. The findings suggest that immune activation affects fatigue severity and possibly other behavioral responses, offering important information when providing care to patients with persistent radiculopathy. The integration of biobehavioral nursing interventions in pain management may have a greater impact on quality of life than treatment focused only on pain.

Fatigue is a common and disabling symptom in patients with neuropathic pain (NP), and it can negatively affect activities of daily living, psychosocial engagement, and participation in therapeutic treatments (Jensen, Chodroff, & Dworkin, 2007; Reyes-Gibby, Mendoza, Wang, Anderson, & Cleeland, 2003; Smith, Torrance, Bennett, & Lee, 2007; Wallace, 2005). Individuals with NP regard reduced fatigue, secondary to pain relief, as the most important indicator of treatment success (Brown et al., 2008; Robinson et al., 2005). Although it is estimated that up to 55% of persons with chronic pain experience fatigue, it is a symptom that often receives little attention in clinical practice (Mota & Pimenta, 2006). In contrast with musculoskeletal pain, fatigue associated with NP tends to persist despite improvements in pain intensity (Meyer-Rosberg et al., 2001).

As a subjective experience, fatigue may include both psychologic and physical attributes (Aaronson et al., 1999). Conceptually, fatigue is defined as “extreme and persistent tiredness, weakness, or exhaustion—mental, physical, or both” (Dittner, Wessely, & Brown, 2004, p. 157). Fatigue is classified as persistent or chronic when there are multiple, additive,

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or unknown causes and duration of symptoms exceeds 6 months (Piper, 1989). Exact mechanisms of NP-related fatigue remain unclear, although research suggests that psychosocial and physiologic factors may predispose certain individuals to persistent fatigue.

PSYCHOSOCIAL PREDICTORS OF FATIGUE

Early research on the relationship between pain and fatigue identified depression as a major mediating factor (Covington, 1991;Feuerstein, Carter, & Papiak, 1987;Hawley & Wolfe, 1997). More recently, Fishbain et al. (2003) performed a structured evidence-based review of the literature to determine the association between chronic pain and fatigue. Three consistent findings were identified. Fatigue development follows pain onset, duration of pain predicts the presence of fatigue, and higher pain severity increases the chances of fatigue. The authors suggested that a common etiology could underlie the association between pain and fatigue.

An exploratory study among 218 patients with chronic pain by Fishbain et al. (2004) found that fatigue was significantly higher in patients with chronic pain than in control subjects (nonpatients). The presence of fatigue was predicted by four major variables: the presence of neuropathic pain, female gender, the presence of depression, and the number of psychiatric diagnoses. Fatigue is one of the most common symptoms of a depressive episode (Maletic et al., 2007). However, recent evidence indicates that depressive symptoms, even when not qualifying as clinical depression, can have a similar impact in mediating poor outcomes across a range of medical conditions (Kiecolt-Glaser & Glaser, 2002).

Although such studies have made important strides in describing the negative impact of fatigue and identifying risk factors in patients with chronic pain, few studies have focused on potential physiologic processes or biologic factors that may affect fatigue severity. Accumulating evidence in other populations suggests that fatigue may develop secondary to enduring immune activation (Bower, Ganz, Aziz, & Fahey, 2002; Capuron et al., 2002; Collado-Hidalgo, Bower, Ganz, Cole, & Irwin, 2006). In the development of NP, injury to neural tissue is followed by increased release of proinflammatory cytokines, which in turn, activate inflammatory processes. In particular, interleukin (IL) 6 plays a significant role in adaptive immunity and the transition to chronic inflammation. Moreover, elevated levels of IL-6 can induce a variety of behavioral responses, including fatigue, and is associated with depressive symptoms (Maier & Watkins, 1998). A deeper understanding of the relationships among biologic factors of immune activation and psychologic and behavioral responses in persons with NP may translate into improved methods for assessing and treating fatigue.

BIOLOGIC FACTORS AND FATIGUE

Fatigue in medically ill populations may develop secondary to the disease process, and a high prevalence of persistent fatigue is found among persons with cancer, congestive heart failure, and rheumatoid arthritis (Chen, 1986). It may also be related to clinical conditions such as hypothyroidism and anemia, as well as to medications (such as antidepressants, anticonvulsants, or opioids) or lack of physical activity. Although the prevalence of fatigue in persons with NP is well recognized, the etiology remains poorly understood and no consistent physiologic factors have been identified (Cathebras, Robbins, Kirmayer, & Hayton, 1992).

In contrast, studies using a “cytokine-induced sickness behavior” framework have provided some evidence of the association between proinflammatory cytokines and fatigue, as well as other negative symptoms (Watkins, Milligan, & Maier, 2003). Proinflammatory cytokines are small proteins released by immune cells and injured tissue, and include IL-1β, IL-6, and

tumor necrosis factor α. A recent study found that persistent fatigue in breast cancer survivors was associated with immune activation modulated through the increased release of IL-6 and elevated levels of soluble IL-6 receptor (sIL-6R) (Collado-Hidalgo et al., 2006), which amplifies the inflammatory actions of IL-6 by forming a complex with it that prolongs its biologic activity and allows it to act on cells that are not normally responsive to it. Similarly to IL-6, levels of sIL-6R increase in response to physical and/or psychologic stress and emotions (Friedman, Hayney, Love, Singer, & Ryff, 2007).

Numerous studies implicate IL-6 as a significant mediator in the development and maintenance of NP within the central nervous system (Abbadie, 2005; Bolin, Verity, Silver, Shooter, & Abrams, 1995; Murphy et al., 1999; Obreja, Schmelz, Poole, & Kress, 2002). Increased central cytokine levels can influence regulation of the hypothalamic-pituitary-adrenal (HPA) axis and lead to alterations in circulating IL-6 activity(De Jongh et al., 2003; DeLeo, 2006; Lee, Lee, Son, Hwang, & Cho, 2004). In turn, elevated circulating levels of cytokines can affect psychologic and behavioral responses, including psychologic distress and depressive symptoms, which can lead to reduced quality of life (Lekander, Elofsson, Neve, Hansson, & Unden, 2004; Siedlecki, 2006). For example, significant relationships among IL-6, psychologic distress, and mood disturbance were found in patients with chronic low back pain (Starkweather, Witek-Janusek, Nockels, Peterson, & Mathews, 2005), and the association between IL-6 and depression has been well documented (Maletic et al., 2007; Strouse, 2007; Vollmer-Conna et al., 2004).

Noting the high prevalence of fatigue in patients with NP, the detrimental impact on quality of life, and a potential biologic mechanism that may influence symptom severity, the purpose of the present descriptive study was to: 1) explore the relationships among fatigue, psychosocial factors (psychologic distress and depressive symptoms), IL-6, and sIL-6R in individuals with NP; and 2) determine the differences in these variables based on fatigue severity. The hypothesis for this study was that systemic levels of IL-6 and sIL-6R in individuals with NP would be significantly related to fatigue severity.

Because various forms of NP have unique personal characteristics and potentially different patterns of immune activation, the selection of a specific NP diagnosis has been recommended when examining biologic variables (Omoigui, 2007). For the present study, individuals with persistent lower extremity radiculopathy (sciatica) caused by nerve impingement were chosen as the target population, because this is a common disorder with a relatively well defined etiology.

THEORETICAL FRAMEWORK

The relationships between fatigue, psychosocial factors, and the selected biologic variables (IL-6 and sIL-6R) were guided by the psychoneuroimmunology (PNI) framework. PNI is “concerned with the mechanisms of multidimensional psychobehavioral-neuroendocrine-immune system interactions” (McCain, Gray, Walter, & Robins, 2005, p. 320). A rich amount of data substantiates the multiple interactions that can occur between psychologic factors and neuroendocrine-immune functioning in healthy and medically ill individuals (Biondi & Picardi, 1999; Witek-Janusek & Mathews, 2000).

In the PNI model, cofactors are those components that have the potential to predispose an individual to certain stressors or health patterns, such as fatigue, and include relevant personal characteristics of the individual, such as gender, age, and the presence of comorbidities. The psychologic component of the model addresses psychobehavioral aspects, including psychologic distress and mood states, which may influence, and be influenced by, biologic factors, such as inflammatory molecules (Chapman, Tuckett, & Song, 2008). A bidirectional relationship exists between the psychologic and biologic

components of the model, and the interactions among patient characteristics and psychosocial and biologic factors ultimately affect health outcomes, including symptom severity and quality of life. From this model, relevant biobehavioral interventions can be developed based on the patient characteristics or psychologic and biologic interactions that are significant to the independent variable.

METHODS

Design and Setting

This study had a descriptive correlational design with 80 adults with persistent radiculopathy. Data were collected from a convenience sample of individuals who were receiving outpatient health care services at three community-based clinics.

Sample and Sampling Criteria

Patients aged 18–60 years with a diagnosis of lower extremity radiculopathy (unilateral and bilateral) caused by nerve impingement (verified by electromyelogram, computerized tomography, or magnetic resonance imaging) who reported symptoms for 6 months or more were invited to participate. Only individuals able to read or speak in English were approached. Patients were excluded from participation if they had a history of cancer, an autoimmune disease, a recent infection, a psychotic disorder or schizophrenia, regular smoking or consumption of >7 alcoholic beverages weekly, or recent laboratory findings (≤1 month) indicating hypothyroidism, renal disease, or anemia, which may indicate a metabolic etiology of fatigue.

Ethical Considerations

The design and implementation of this study was approved by the Institutional Review Boards at each recruitment site, and written consent was obtained from each of the participants.

Measures

Fatigue—Fatigue was assessed using the Profile of Mood States Fatigue/Inertia (POMS-F/I) subscale. This subscale is a part of the 65-item adjective rating scale of the Profile of Mood States (McNair, Lorr, & Droppleman, 1992). The seven-item subscale contains seven adjectives suggesting weariness, inertia, and low energy level. Item responses range from 0 (not at all) to 4 (extremely) on a 5-point scale, and totaled subscale scores range from 0 to 28. Each scale item is a symptom of fatigue. Higher total scores indicate greater levels of fatigue. Based on past research that demonstrated significant quality of life differences according to fatigue severity (Dirksen, Belyea, & Epstein, 2009), dummy coded variables for low fatigue (score 0–6), moderate fatigue (7– 17), and high fatigue (score 18–28) were assigned based on the participant's totaled score. The POMS-F/I demonstrates test-retest reliability, internal consistency, and concurrent and construct validity (McNair, Lorr, & Droppleman, 1992). In the present study, Cronbach α was 0.92.

Pain Perception—The McGill Pain Questionnaire Short Form (MPQ-SF) is a reliable self-report measure of pain perception (Melzack, 1987). It entails fifteen verbal descriptors of sensory and affective dimensions of pain and is scored on a 4-point scale from 0 (none) to 3 (severe) by adding the numeric value of each pain dimension. Higher scores indicate higher levels of sensory and affective components of pain (range 0–45). Internal consistency of the MPQ is good and test-retest reliability is reported to be between 0.64 to 0.87 (Melzack & Katz, 2001). The reliability of the MPQ-SF for this study was α = 0.85.

Psychologic Distress—The Perceived Stress Scale (PSS) is the most widely used psychologic instrument for measuring psychologic distress. PSS is a brief tenitem scale measuring the degree to which experiences are appraised as uncontrollable (Cohen, 1994). Individuals rate their responses using a 5-point Likert scale. A total score is provided by adding the responses together, with a higher score (0–40) indicating a higher level of psychologic distress. Internal consistency of the PSS ranges from 0.75–0.86, and test-retest reliability is 0.85 (Cohen, 1994).

Depressive Symptoms—The Center for Epidemiologic Studies—Depression (CES-D) scale was used to measure depressive symptoms (Radloff, 1977). The CES-D is a 20-item instrument that rates the frequency of depressive symptoms experienced over the past week using a 4-point scale (0 to 3). Scores can range from 0 to 60, with higher scores indicating higher levels of depressive symptoms. The CES-D has reported reliability of 0.85 in patients with chronic pain (Turk & Okifuji, 1993). In the present study, reliability of the CES-D was 0.88.

IL-6 and sIL-6R—Blood samples were obtained from participants by standard phlebotomy techniques between 8 a.m. and 10 a.m. to control for diurnal variation. Plasma samples were stored at −80°C until analyzed. IL-6 and sIL-6R concentrations were measured in triplicate with enzyme-linked immunosorbent assay (R & D Systems, Minneapolis, MN) according to the manufacturer's directions. Any sample with an optic density greater than that correlating with the highest value on the standard curve was diluted and reassayed. Any sample with an optic density less than that correlating with the lowest value on the standard curve was assigned a value of 0.1 pg/mL (IL-6) or 1.0 pg/mL (sIL-6R). Inter- and intra-assay coefficients of variation for all assays were <7%. Limits of detection were 0.1 pg/ mL for the Quantikine HS IL-6 assay and 1.0 pg/mL for the Quantikine sIL-6R assay.

Data Collection

General demographic information, health, and pain data were obtained during an interview by the investigator at the time of recruitment. Demographic data consisted of age, gender, marital status, race and ethnicity, and education and income levels. Health data consisted of current and past medical history, including diagnoses and medications, height, weight (measured on a calibrated floor scale), and the average amount of exercise per week in minutes. Pain data consisted of duration of pain, usual pain, and worst pain, rated on a scale of 0 to 10. Participants were then asked to complete the self-report instruments (POMS-F/I, MPQ-SF, PSS, and CES-D). Finally, the participant's blood was drawn from an antecubital site, and the specimen was transported directly to the laboratory.

Data Analysis

Data analysis was completed using the Statistical Package for the Social Sciences (SPSS version 16.0; SPSS, Chicago, IL). Descriptive statistics were used to examine the demographic, health, and pain data and totaled scale scores for the entire sample. Bivariate correlations of fatigue and demographic, health, and pain data were analyzed with Pearson product moment correlation and subsequently to test relationships between the main study variables (fatigue, pain, psychologic distress, depressive symptoms, IL-6, and sIL-6R). Multivariate analysis of variance (MANOVA) was conducted to examine the main study variables by subgroup (defined according to degree of fatigue as low, medium, and high). Follow-up one-way analyses of variance (ANOVAs) with Tukey post hoc tests were conducted to examine the individual variables. The IL-6 data were log-transformed for nonuniform residuals. Significance was set at $p = .05$ a priori for all analyses.

RESULTS

Description of Sample

The sample (Table 1) of 80 participants ranged in age from 23–56 years (mean 47, SD 8.9) and was predominately non-Hispanic White (95%), married (65%), and male (52.5%), with an average of 13 years of education (range 11–22). On average, the participants reported that symptoms of sciatica developed over 14 months before the study (range 6–60 months). The mean body mass index of the study sample was 28.5 kg/m^2 (SD 6.5), and most were employed on either a full-time or a part-time basis (62.5%). Hypertension was the most frequently reported comorbidity (67.5%), followed by asthma (10%) and osteoarthritis (7.5%). Most patients reported high levels of usual and worst pain, and the mean pain score on the MPQ-SF was 26 (SD 10.9).

Correlational Analysis

Pearson correlation coefficients were used to examine relationships of demographic, health, and pain data with fatigue. No significant correlations were found for race, marital status, education, income, age, body mass index, weekly exercise, duration of pain, usual pain, or worst pain. When the principle dependent variables for the study were examined (pain intensity, stress, depressive symptoms, IL-6, sIL-6R), a statistically significant relationship was found between fatigue and psychologic distress (r = .681; $p < .001$), depressive symptoms (r = .596; $p < .001$), IL-6 (r = .469; $p < .001$), and sIL-6R (r = .611; $p < .001$), but not pain intensity (r = .206; $p = .066$) (Table 2).

Multivariate Analysis

The MANOVA for the remaining variables (psychologic distress, depressive symptoms, IL-6, sIL-6R) indicated that there were significant differences between subgroups (Wilks λ: $F5,72 = 1865.48$; $p = .001$; Table 3). ANOVAs with Tukey post hoc tests were conducted as a follow-up to MANOVA and revealed significant differences among the subgroups in psychologic stress ($F2,77 = 9.65$; $p = .001$),with the high-fatigue subgroup having significantly greater psychologic distress than the low-fatigue subgroup. Significant differences were also noted for depressive symptoms ($F2,77 = 5.13$; $p = .01$), with the low-fatigue subgroup reporting significantly lower depression scores. Levels of IL-6 were significantly different between subgroups ($F2,77 = 6.21$; $p = .01$), with the moderate- and high-fatigue subgroups having significantly greater IL-6 levels than the low-fatigue subgroup. The high-fatigue subgroup had a significantly higher level of sIL-6R ($F2,77 = 9.11$; $p = .001$) than the moderate- and low-fatigue subgroups.

There were no significant differences among the subgroups on any patient characteristics (Table 4), including age, gender ($\chi^2 = 1.79$; $p = 0.16$), race ($\chi^2 = .057$; $p = 0.92$), education, marital status ($\chi^2 = 1.71$; $p = 0.17$), income ($\chi^2 = 1.67$; $p = 0.19$), and employment ($\chi^2 = 4.72$; $p = 0.54$). Likewise, there were no group differences for body mass index,comorbid conditions, medications ($\chi^2 = 3.67$; $p = 0.09$), weekly exercise ($\chi^2 = 1.67$; $p = 0.19$), duration of pain, usual pain, or worst pain.

DISCUSSION

High levels of fatigue were found in this sample of patients with persistent radiculopathy (27.5% low, 32.5% moderate, 40% high). The bivariate analysis showed that fatigue was significantly correlated with psychologic distress, depressive symptoms, IL-6, and sIL-6R. Similarly to earlier studies, the level of fatigue was not correlated with pain intensity (Fishbain et al., 2004; Fishbain et al., 2005). Although it is commonly thought that patients with elevated pain levels are more likely to experience fatigue, the results imply that fatigue

can occur across a wide range of pain levels. This finding strengthens the case for incorporating the assessment of fatigue into routine management of NP so that it can be adequately addressed in the plan of care. It also implies that different therapeutic strategies may be needed to decrease fatigue levels beyond interventions focused solely on reducing pain intensity.

The differences between the fatigue-based subgroups on psychologic and biologic factors suggest that fatigue, depressive symptoms, and psychologic distress may co-occur as part of a coordinated response to elevated IL-6 and sIL-6R. It also informs nursing that the presence of depressive symptoms and psychologic distress are likely to occur as fatigue levels increase. Participants with the highest fatigue severity scores had significantly higher levels of sIL-6R, which is thought to enable IL-6 to gain increased (feedback) control over central nervous mechanisms regulating behavioral responses, such as depressive symptoms. Conversely, increased levels of psychologic distress may influence the HPA axis and lead to alterations in circulating IL-6 activity (De Jongh et al., 2003; DeLeo, 2006; Lee, Lee, Son, Hwang, & Cho, 2004). More research is necessary to determine whether nursing interventions that target stress and/or depressive symptoms in this patient population affect IL-6 activity and reduce fatigue. However, research exploring biobehavioral interventions in other populations appears to be promising. For instance, Morone, Lynch, Greco, Tindle, and Weiner (2008) used mindfulness meditation among older adults with chronic pain and found an immediate effect on mood elevation as well as long-term global effects on fatigue and quality of life. Mindfulness-based therapies have been shown to be successful in augmenting traditional treatment strategies for depression (Scherer-Dickson, 2004), and improving coping and well-being in patients with immune-related disease (Robins et al., 2006).

Participant characteristics did not further distinguish the subgroups, which was somewhat unexpected. Research has noted in persons with NP that significant relationships exist among symptom reporting and demographic and clinical characteristics, including age, gender, marital status, employment, and duration of pain (Fishbain et al., 2005). The strength of the relationships may be attributed to the homogeneity in sample characteristics, NP diagnosis, and/or duration of pain.

Although these findings do not establish that the differences in psychologic distress or depressive symptoms were caused by increased levels of IL-6 and sIL-6R, earlier research has linked elevated IL-6 levels with prolonged psychologic distress, lower quality of life, and increased morbidity and mortality (Lutgendorf et al., 1999; Miller, Cohen, & Ritchey, 2002) as well as with depression (Maletic et al., 2007; Strouse, 2007; Vollmer-Conna et al., 2004). Another plausible cause of immune disturbance and subsequent fatigue in NP is pain treatment. However, there was no evidence that a specific type of medication accounted for group difference in fatigue or IL-6 levels. In fact, several classes of medications used to treat NP, such as opioids and tricyclic antidepressants are thought to reduce systemic levels of IL-6 (Attal et al., 2006; Stillman, 2006). Finally, recent evidence indicates that a common variant of the IL-6R gene results in major changes in circulating levels of IL-6 and IL-6R (Rafiq et al., 2007). Genetic biomarkers may provide useful information in explaining the variations in neural-immune processes after nerve injury and may, in the future, be used to predict symptom manifestations and guide more individually tailored interventions. Future research focused on the mechanisms underlying fatigue,or that test biobehavioral interventions targeting fatigue in individuals with NP, may consider including genetic biomarkers that regulate IL-6 activity.

Limitations

The present study had several limitations, most notably the relatively small sample size in a population of mostly non-Hispanic White individuals. The cross-sectional design and

convenience sampling used limits the generalization of findings to patients with lower extremity radiculopathy, and no causal relationships can be implied. In addition, IL-6 and sIL-6R were the only measures of immune activation measured, and other research has shownthat IL-6 can influence levels ofother pro- and antiinflammatory molecules that may be involved in the experience of fatigue (Watkins, Milligan, & Maier, 2003).

Nursing Implications

The high levels of fatigue in the present study suggest that nurses proactively assess for the presence of fatigue in patients with NP, even when pain levels are low or decreasing. Further research on biobehavioral nursing interventions, such as mindfulness meditation, that have been shown to reduce fatigue, psychologic distress, and depressive symptoms, need to be examined in fatigued patients with NP. The greatest positive effect on quality of life may be derived from integrative multimodal therapeutic approaches that address a group of symptoms commonly experienced in persons with NP (fatigue, psychologic distress, and depressive symptoms) rather than treatment focused on reducing pain intensity alone.

CONCLUSIONS

The high rate ofmoderate to severe fatigue in the present sample supports the inclusion of fatigue assessment in routine management of NP. Differences in psychologic and biologic factors between fatigue-based subgroups suggest that immune activation, as seen by elevated IL-6 and sIL-6R levels, affects fatigue severity. The identification of fatigue-based subgroup characteristics may help to guide future interventions based on fatigue levels, such as assessing and treating depressive symptoms and psychologic stress using integrative strategies. Biobehavioral nursing interventions that target depressive symptoms and/or psychologic distress need to be examined in this patient population so that we may begin to understand the complex interrelationships between symptoms. Fatigued patients with persistent radiculopathy may benefit by a shift of focus from treatment concentrating on pain relief alone to a tailored intervention that targets multiple symptoms so that better symptom management, quality of life, and treatment outcomes may be attained.

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Table 1

Characteristics of the Sample

Gender	38 (47.5%) women, 42 (52.5%) men
Race	95% non-Hispanic White, 5% African American
Age (y)	23–56 (mean 47, SD 8.9)
Education (y)	11–22 (mean 13, SD 4.5)
Marital status	52 (65%) married, 28 single (32.5% divorced, 2.5% widowed)
Income	25 (31%) <$40,000/y, 6 (7.5%) <$20,000/y
Employment	50 (62.5%) employed full- or part-time
Body mass index (kg/m^2)	22–48 (mean 28.5, SD 6.5)
Weekly exercise (min)	0–120 (mean 48.9, SD 24.6)
Comorbid conditions	54 (67.5%) hypertension, 8 (10%) asthma, 6 (7.5%) osteoarthritis
Medications	10 (12.5%) opioids, 22 (27.5%) neuroleptics, 26 (32.5%) antidepressants, 9 (11.3%) muscle relaxants
Duration of pain (mo)	6–60 (mean 14, SD 6.2)
Usual pain	4–10 (mean 6.2, SD 1.75)
Worst pain	7–10 (mean 9.1, SD .96)

Table 2

Correlations among Fatigue, Psychologic Distress, Depression, IL-6, and sIL-6R

	Pain Intensity	Psychologic Distress	Depressive Symptoms	IL-6 (pg/mL)	sIL-6R (pg/mL)	Fatigue
Pain intensity	1.0					
Psychologic distress	.416*	1.0				
	.019					
Depressive symptoms	.427*	.599**	1.0			
	.024	.001				
IL-6 (pg/mL)	.193	.459**	.473**	1.0		
	.218	.006	.002			
sIL-6R (pg/mL)	.162	.493**	.452*	.792**	1.0	
	.265	.001	.031	.001		
Fatigue	.206	.681**	.596**	.469**	.611**	1.0
	.066	.001	.001	.001	.001	

*Significance at $p < .05$ (two-tailed).

**Significance at $p < .01$ (two-tailed).

Table 3

Study Variable Means (SD) for the Three Subgroups

Variable	Low Fatigue (n = 22)	Moderate Fatigue (n = 26)	High Fatigue (n = 32)	F	*p* Value	Results
Psychologic distress (PSS)	14.6 (5.6)	19.5 (4.9)	29.3 (6.8)	9.65	.001	L<M<H
Depressive symptoms (CES-D)	5.3 (2.9)	12.1 (3.1)	13.5 (1.7)	5.13	.01	L<M,H
IL-6 (pg/mL)	1.6 (1.01)	2.7 (1.12)	3.3 (1.6)	6.21	.01	L<M,H
sIL-6R (pg/mL)	654.1 (222.4)	771.2 (226.7)	854.6 (230.1)	9.11	.001	L<M<H

Table 4

Participant Scores [Mean (SD)] on Demographic and Clinical Characteristics for the Three Subgroups

Characteristic	Low Fatigue (n = 22)	Moderate Fatigue (n = 26)	High Fatigue (n = 32)	F	*p* Value
Age (y)	44.8 (10.3)	47.8 (9.3)	45.2 (8.8)	1.36	.144
Education (y)	12.8 (1.9)	12.5 (1.7)	12.3 (2.4)	0.386	.681
No. of comorbidities	1.4 (1.1)	1.2 (1.0)	1.7 (1.2)	1.05	.218
Body mass index (kg/m^2)	28.4 (2.9)	30.1 (8.9)	28.5 (5.7)	1.98	.544
Duration of pain (mo)	12.9 (3.4)	14.8 (3.8)	13.6 (3.2)	0.211	.758
Usual pain	6.1 (2.2)	6.3 (2.4)	5.9 (1.8)	1.99	.142
Worst pain	9.2 (3.1)	8.9 (2.2)	9.0 (2.8)	0.254	.726