Title
Gender Differences in the Occurrence and Severity of Anxiety, Depression, and Fatigue in Oncology Patients at the Initiation of Radiation Therapy

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Gender Differences in the Occurrence and Severity of Anxiety, Depression, and Fatigue in Oncology Patients at the Initiation of Radiation Therapy

by

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Abstract

Background Research has determined that anxiety, depression, and fatigue are common problems in oncology patients, and may have negative effects on patients' quality of life (QOL). However, research on gender differences for these symptoms is limited. The purpose of this study was to evaluate for gender differences in occurrence rates and severity of anxiety, depression, fatigue and energy at the initiation of RT, and also evaluate for gender differences in QOL. **Methods** Participants (n=183) undergoing primary or adjuvant RT were recruited from two RT departments located in a Comprehensive Cancer Center and a community-based oncology program at the time of the patient's simulation visit. Symptoms and QOL were evaluated using the Spielberger State-Trait Anxiety Inventories (STAI-T and STAI-S), the Center for Epidemiologic Studies-Depression (CES-D) Scale, the Lee Fatigue Scale (LFS), and the Quality of Life-Scale-Patient Version (QOL-PV). Statistical analysis was performed by SPSS 15. Independent sample t-tests and Chi Square analyses were used to evaluate for gender differences in demographic and clinical characteristics. In addition, age was entered as a covariate in the univariate analyses of variance that evaluated for gender differences in symptom and QOL scores. **Results** The results showed that women reported higher occurrence rates for state anxiety, depression, and lower levels of morning energy compared to men. Women also reported greater severity of depression, evening fatigue, and poorer psychological and physical QOL. **Conclusion** Findings from this study suggest that gender may influence patients' symptom experience and QOL. Further investigation is warranted to confirm the findings from this study and to understand the biological, psychological, and social factors that contribute to these differences.

Tables

Figures

Introduction

A significant amount of research has determined that anxiety [1, 2], depression [1, 3], and fatigue [4-7] are common problems in oncology patients. In addition, all three symptoms have negative effects on patients' quality of life (QOL) [8, 9]. While findings from population studies suggest that these symptoms are more common [10] and severe [11] in women, only a limited amount of research is available on gender differences in the occurrence rates for and severity of fatigue, depression, and anxiety in oncology patients at the initiation of radiation therapy (RT).

A substantial body of evidence suggests that fatigue occurs in 31% to 100% of patients during RT [4, 5, 7, 12]. However, studies that evaluated for gender differences in fatigue during or immediately following cancer treatment have produced conflicting evidence. In three studies, women reported higher fatigue severity scores [11, 13, 14], while no differences were found in three other studies [15-17]. These inconsistencies across studies may be related to the characteristics of the patients (i.e. differences in social support or clinical characteristics), measures used to evaluate fatigue, or the timing of the measures.

Clinically significant depression occurs in up to 24% of oncology patients [1, 2, 18]. However, only seven studies were found that evaluated for gender differences in depression in oncology patients. Consistent with population-based studies [19-21], four studies found that women had higher depression scores [22, 23] while three studies found no gender differences in the severity of depression

[24-26]. While higher rates of depression are documented in women in the general population [20, 27, 28], additional research is warranted on gender differences in depression in oncology patients.

While less studied, clinically significant levels of anxiety occur in 21% to 38% [1, 29] of oncology patients, while one study reported rates as high as 62% [30], indicating variability based on cancer site. As with fatigue and depression, studies of gender differences in anxiety have produced conflicting results. While three studies found no gender differences in anxiety in cancer patients [2, 31, 32], in one study, female cancer patients sought out more help when anxious or distressed [33]. Again, these conflicting results may be related to the instruments used to measure anxiety and the timing of the assessments.

Each oncology patient has a unique experience with their respective treatment that has a differential impact on their QOL [34, 35]. In the limited number of studies of gender differences in QOL in oncology patients, women reported a poorer QOL than men, that was associated with higher levels of depression [36] or decreased physical function [37]. In contrast, no gender differences in QOL were found in another study of patients with a variety of cancer diagnoses [38]. While QOL has become an important outcome in oncology research [39, 40], gender differences in the various domains of QOL prior to RT have not been evaluated.

Given the paucity of research on gender differences in symptoms and QOL in oncology patients, the purpose of this study was to evaluate for gender differences in occurrence rates and severity of anxiety, depression, fatigue, and

energy at the initiation of RT. In addition, gender differences in QOL were evaluated in these patients.

Methods

Participants and Settings - This descriptive, correlational study is part of a larger, longitudinal study that evaluated multiple symptoms in patients who underwent primary or adjuvant RT [41, 42]. A total of 183 patients were recruited from two RT departments located in a Comprehensive Cancer Center and a community-based oncology program at the time of the patient's simulation visit.

Patients were eligible to participate if they were ≥18 years of age; were scheduled to receive primary or adjuvant RT for one of four cancer diagnoses (i.e., breast, prostate, lung, brain); were able to read, write, and understand English; gave written informed consent; and had a Karnofsky Performance Status (KPS) score of≥ 60. Patients were excluded if they had metastatic disease; more than one cancer diagnosis; or a diagnosed sleep disorder.

Instruments – The study instruments included a demographic questionnaire, the KPS scale [43], the Spielberger State-Trait Anxiety Inventories (STAI-T and STAI-S) [44], the Center for Epidemiologic Studies-Depression (CES-D) Scale [45], and the Lee Fatigue Scale (LFS) [46]. QOL was measured using the Quality of Life-Scale-Patient Version (QOL-PV) [47, 48].

The demographic questionnaire obtained information on age, gender, marital status, education, ethnicity, employment status, and the presence of a number of co-morbid conditions.

The STAI-T and STAI-S inventories consist of 20 items each that are rated from 1 to 4. The scores for each scale are summed and can range from 20 to 80. A higher score indicates greater anxiety. The STAI-T measures an individual's predisposition to anxiety determined by his/her personality and estimates how a person generally feels. The STAI-S measures an individual's transitory emotional response to a stressful situation. It evaluates the emotional responses of worry, nervousness, tension, and feelings of apprehension related to how a person feels "right now" in a stressful situation. Cutoff scores of $\geq$31.8 and $\geq$32.2 indicate high levels of trait and state anxiety, respectively. The STAI-S and STAI-T inventories have well-established criterion and construct validity and internal consistency reliability coefficients [44, 49, 50]. In the current study, the Cronbach's alphas for the STAI-T and STAI-S were 0.92 and 0.95, respectively.

The CES-D consists of 20 items selected to represent the major symptoms in the clinical syndrome of depression. Scores can range from 0 to 60, with scores of $\geq$16 indicating the need for individuals to seek clinical evaluation for major depression. The CES-D has well-established concurrent and construct validity [45, 51, 52]. In the current study, the Cronbach's alpha for the CES-D was 0.88.

The LFS consists of 18 items designed to assess physical fatigue and energy [46]. Each item was rated on a 0 to 10 NRS. Total fatigue and energy scores were calculated as the mean of the 13 fatigue items and the 5 energy items, with higher scores indicating greater fatigue severity and higher levels of energy. Respondents were asked to rate each item based on how they felt "right now," within 30 minutes of awakening (morning fatigue, morning energy), and prior to

going to bed (evening fatigue, evening energy). The LFS has been used with healthy individuals [46, 53] and in patients with cancer and HIV [7, 54-56]. Cutoff scores of $\geq$3.2 and $\geq$5.6 indicated high levels of morning and evening fatigue, respectively [41]. Cutoff scores of $\leq$6.0 and $\leq$3.5 indicate low levels of morning and evening energy, respectively. The LFS was chosen for this study because it is relatively short, easy to administer, and has well established validity and reliability. In this study, Cronbach's alphas for evening and morning fatigue were 0.96 and 0.95, respectively. Cronbach's alphas for evening and morning energy were 0.95 and 0.96, respectively.

The QOL-PV is a 41-item instrument that measures four dimensions of QOL in cancer patients (i.e. physical well-being, psychological well-being, spiritual well-being, social well-being) as well as a total QOL score. Each item is scored on a 0 to 10 scale with higher scores indicating a better QOL. The QOL-PV has established validity and reliability [47, 48, 57, 58]. In the current study, the Cronbach's alpha for the QOL-PV total score was 0.94.

Study Procedures - The study was approved by the Committee on Human Research at the University of California, San Francisco and the IRB at the second site. At the time of the simulation visit (i.e., approximately one week prior to the initiation of RT), patients were approached by a research nurse to discuss participation in the study. After obtaining written informed consent, patients completed the demographic questionnaire and KPS scale [43], the STAI-T and STAI-S [44], and CES-D [45]. In addition, patients were taught to complete the LFS [46] before going to bed each night (i.e., evening fatigue, evening energy)

and upon arising each morning (i.e., morning fatigue, morning energy) for 2 consecutive days. Patients were asked to return the questionnaires to the research nurse in the RT department at the completion of the two days of data collection.

Data Analysis - Data were analyzed using SPSS version 15. Descriptive statistics and frequency distributions were generated for the sample characteristics and symptom data. Independent sample t-tests and Chi Square analyses were used to evaluate for gender differences in demographic and clinical characteristics. In addition, gender differences in occurrence rates for trait anxiety (i.e. STAI-T score $\geq$31.8), state anxiety (i.e. STAI-S score $\geq$32.3), depression (i.e. CES-D score $\geq$16.0) evening fatigue (i.e. LFS score $\geq$5.6), morning fatigue (i.e. LFS score $\geq$3.2), evening energy (Lee Energy Score $\leq$3.5), and morning energy (i.e. Lee Energy Score $\leq$6.0) were evaluated using Chi Square analysis. Based on the analysis of demographic characteristics, female patients were found to be significantly younger than male patients. A number of studies have shown that there is a relationship between age and fatigue [59, 60], depression [61], and anxiety [62]. Therefore, age was entered as a covariate in the univariate analyses of variance that evaluated for gender differences in symptom and QOL scores. All calculations used actual values. Adjustments were not made for missing data. Therefore, the cohort for each analysis was dependent on the largest set of available data across groups. A p-value of <0.05 are considered statistically significant.

Results

Gender Differences in Demographic and Clinical Characteristics

As shown in Table 1, 87 female and 96 male patients participated in this study. No differences were found, between the female and male patients, in any demographic or clinical characteristics except for age, marital status, employment, living arrangements, diagnosis, time since diagnosis, and KPS score. Female patients were significantly younger ($p<0.0001$), more likely to live alone ($p=0.026$), and less likely to be married ($p<0.0001$) than male patients. In terms of diagnosis, a higher percentage of female patients had breast cancer while a higher percentage of male patients had prostate cancer ($p<0.0001$). In addition, female patients reported a shorter time since diagnosis and a worse KPS score (both $p<0.0001$).

Gender Differences in Symptom Occurrence Rates

As shown in Figure 1, no gender differences were found in occurrence rates for trait anxiety ($p=0.10$), evening fatigue ($p=0.06$), morning fatigue ($p=0.06$), and low levels of evening energy ($p=0.15$) based on clinically meaningful cut-point scores. However, females had significantly higher occurrence rates of state anxiety ($p=0.04$), depression ($p=0.001$), and low levels of morning energy ($p=0.007$) compared to males.

Gender Differences in Anxiety and Depression Scores

As shown in Figure 2, after controlling for age, no differences in STAI-T or STAI-S scores were found between female and male patients. In contrast, female patients reported significantly higher CES-D scores than male patients.

Gender Differences in Fatigue and Energy Scores

As shown in Figure 3, after controlling for age, female patients reported significantly higher evening fatigue scores than male patients ($p=0.004$). However, no gender differences were found in patients' ratings of morning fatigue, evening energy, or morning energy.

Gender Differences in QOL Scores

As shown in Figure 4, after controlling for age, no differences were found in female and male patients scores on the social and spiritual subscales of the QOL-PV or in its total QOL score. However, female patients reported significantly lower scores for the physical and psychological subscales of the QOL-PV (both $p<0.02$).

Discussion

This study is the first to evaluate for gender differences in occurrence rates and severity scores for anxiety, depression, fatigue, and energy, as well as ratings of QOL in the same sample of patients at the initiation of RT. Based on the use of clinically meaningful cut-points, while symptom occurrence rates were relatively high for both genders, occurrence rates for state anxiety, depression, as well as low levels of morning energy were significantly higher for female compared to male oncology patients. In addition, female patients reported significantly higher levels of depression and evening fatigue.

The occurrence rates for clinically significant state and trait anxiety in both women (45.9%, 62.1% respectively) and men (30.5%, 49.0% respectively) were

similar to the rates found in previous studies of patients undergoing RT [1, 2, 63]. In addition, while no gender differences were found in the levels of trait and state anxiety, mean scores for both females and males were above the cut-points for clinically meaningful levels of anxiety. The high levels of anxiety at the initiation of RT are consistent with previous reports [64-66] and expected given the fact that patients are starting a new phase of treatment. While fewer studies have examined anxiety compared to depression in oncology patients, the high levels of anxiety in both genders is of concern because high levels of anxiety result in sleep disturbance [67-69], increased fears of disease progression [70], dose delays or reduction in cancer treatment [71], and decreased communication with physicians [72].

The fact that women reported higher rates of occurrence as well as severity scores for depression is consistent with previous reports in oncology patients [10, 23]. In fact, the occurrence rate for clinically significant levels of depressive symptoms was almost 3 times higher in the women (34.5%) compared to the men (12.8%). While both genders' mean CES-D scores were below the score of 16, women reported significantly higher scores than men. The gender differences in depressive symptoms found in this study may be partially explained by several gender differences in demographic and clinical characteristics. For example, previous studies have found higher levels of depressive symptoms in younger oncology patients [23, 56, 73] as well as in patients with poor functional status [6, 16] and greater levels of reported pain [74]. In addition, compared to the male patients, women in this study were more

likely to be unmarried and living alone, which might reflect a decrease in social support. This finding warrants additional investigation because lower levels of social support were associated with higher levels of depressive symptoms in previous studies of oncology patients [75-78].

Most studies of cancer-related fatigue have not evaluated for diurnal variability in either the occurrence or severity of this symptom. As expected, fatigue severity was higher in the evening than in the morning in both men and women. However, consistent with previous studies [13, 14], women reported higher levels of fatigue that approached the LFS cutoff score of ≥ 5.6. This gender difference in evening fatigue severity may be explained by the fact that women in this study had a poorer KPS score, were less likely to be married, and more likely to live alone. In fact, previous studies have found increased levels of fatigue in oncology patients with poor functional status [79-82] and those with less social support [29, 83, 84].

An equally important finding is that while no gender differences were found in the occurrence rates for evening and morning fatigue, between 31.4% (evening) and 39.5% (morning) of women and 18.9% (evening) and 25.3% (morning) of men reported clinically significant levels of these two symptoms. While these fatigue occurrence rates are similar to previous RT studies [5, 12, 85], these rates are relatively high when one considers that these patients are about to commence RT. In addition, in both genders, the occurrence rates for clinically significant levels of morning fatigue were higher than for evening fatigue. This finding may be partially explained by the higher levels of sleep

disturbance in both men and women at the initiation of RT (Garrett et al., in review).

The National Comprehensive Cancer Network's Practice Guideline on Cancer-related Fatigue [86] recommends and one study has evaluated [87] the use of energy conservation techniques to decrease cancer-related fatigue. However, to our knowledge, this study is the first to evaluate for gender differences in the occurrence of low levels of morning and evening energy as well as diurnal variability in energy scores in patients at the initiation of RT. In the original validation study of the LFS [46], the energy subscale was a distinct factor from the fatigue subscale. In addition, significant correlations were found between healthy subjects' ratings of morning ($r=0.80$) and evening ($r=0.45$) energy and the vitality subscale of the Profile of Mood States. Compared to healthy participants, oncology patients in this study reported significantly higher evening energy scores (4.48 versus 3.49, $p<0.001$), but lower morning energy scores (5.73 versus 6.03, $p=0.04$). While it is surprising that the oncology patients reported higher levels of evening energy than the healthy individuals in Lee's study, it is consistent with her findings that patients with sleep disorders reported higher levels of evening energy, but lower levels of morning energy than her healthy controls. Additional research is warranted in oncology patients to evaluate for diurnal variability in levels of energy, how energy levels correlate with fatigue severity, and how fatigue and energy levels change over the course of RT.

While the findings on gender differences in QOL among oncology patients are inconclusive [37, 38], findings from this study suggest that women and men may differ on their appraisal of the various dimensions of QOL. While total QOL scores were not different, women reported poor physical and psychological subscale scores on the QOL-PV. These findings are consistent with the poorer functional status and higher depression scores reported by women in this study. In addition, the subscale and total QOL scores for patients in this study are similar to those reported by patients with thyroid [88] and ovarian [89] cancer and long-term cancer survivors [90] using similar versions of the QOL measure used in this study. Additional research is needed to determine whether gender differences exist in the predictors of QOL in oncology patients at the initiation of RT.

Several study limitations need to be acknowledged. While the overall sample size was relatively large, additional gender differences in symptoms and QOL may be identified with larger samples. Because the majority of the female patients had breast cancer and the majority of male patients had prostate cancer, the gender differences identified in this study may not be generalizable to other cancer diagnoses. Additional research is warranted to identify gender-specific and disease-specific predictors of symptoms and QOL.

Despite these limitations, findings from this study suggest that gender may influence patients' perceptions of symptoms and QOL. Further research is necessary to confirm the findings from this study and to understand the biological, psychological, and social factors that contribute to these differences.

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Table 1. Differences in Demographic and Clinical Characteristics Between Female (n=87) and Male (n=96) Patients

	Females	Males	Statistics
Characteristic	Mean (SD)	Mean (SD)	t value, p value
Age (years)	54.7 (11.9)	66.0 (9.4)	-7.134, p<0.001
Education (years)	16.2 (2.7)	15.9 (3.2)	0.784, 0.434
Karnofsky Performance Status	87.4 (12.6)	93.8 (9.8)	-3.771, p<0.001
Number of comorbidities	5.0 (2.5)	4.6 (2.5)	1.044, 0.298
Time since diagnosis (months)	4.8 (2.8)	8.5(12.5)	-2.835, p<0.001
	n (%)	n (%)	
Ethnicity			
White	61 (70.1)	71 (74.0)	p=0.622
Non-white	26 (29.9)	25 (26.0)	
Lives alone			
Yes	34 (38.2)	22 (22.9)	p=0.026
No	55 (61.8)	74 (77.1)	
Marital status			
Married	35 (40.7)	68 (70.8)	p<0.001
Not married	51 (59.3)	28 (29.2)	
Employment			
Yes	38(43.7)	41(44.6)	p=0.512
No	49(56.3)	51(55.4)	
Diagnosis			
Breast	78 (87.6)	0 (0.0)	
Prostate	0 (0.0)	82 (85.4)	X^2=167.23,p<0.001
Lung	9 (10.1)	4 (4.2)	
Brain	2 (2.2)	10 (10.4)	

Figure 1 – Gender differences in symptom occurrence rates of clinically significant levels of anxiety, depression, fatigue, and low levels of energy.

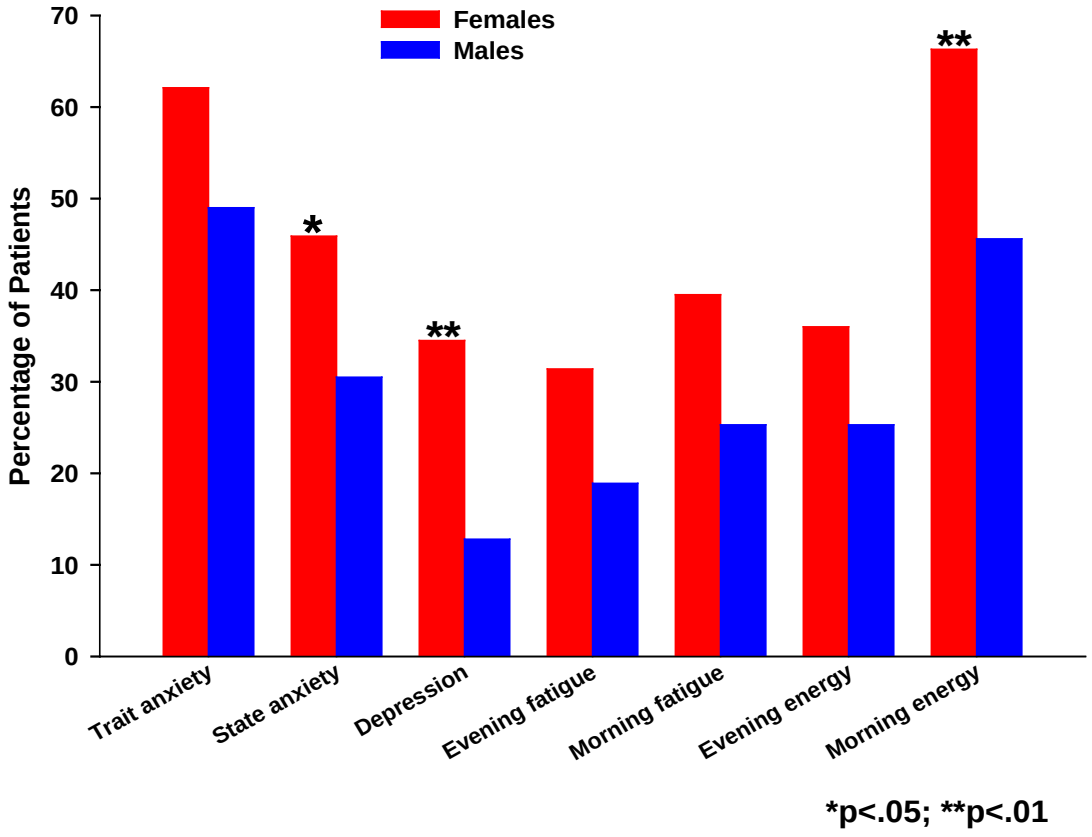


Figure 2 – Gender differences in anxiety (A) and depression (B) scores. All values are plotted as means ± standard errors of the mean.

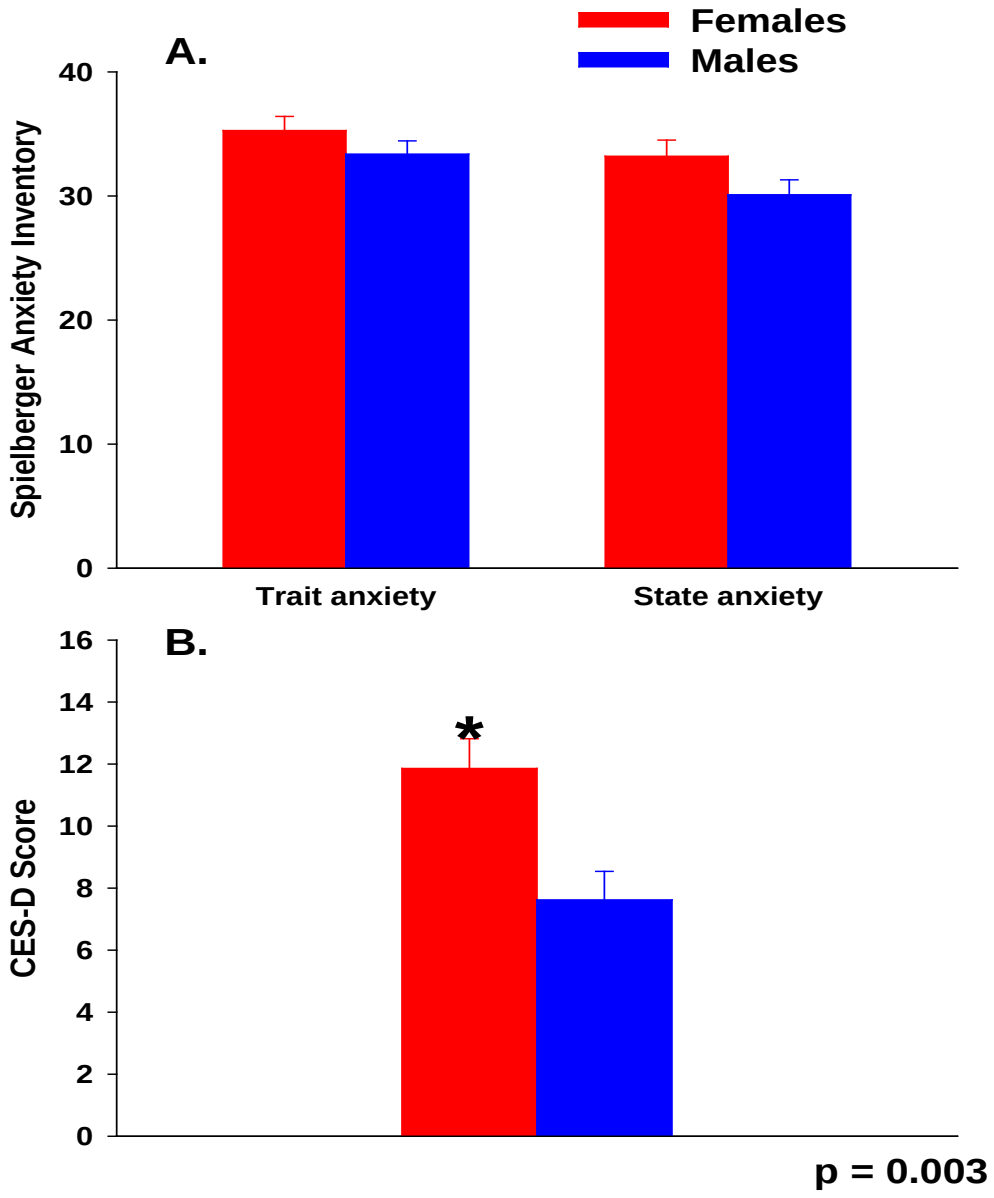


Figure 3 – Gender differences in evening and morning fatigue severity (A) and evening and morning energy levels (B). All values are plotted as means ± standard errors of the mean.

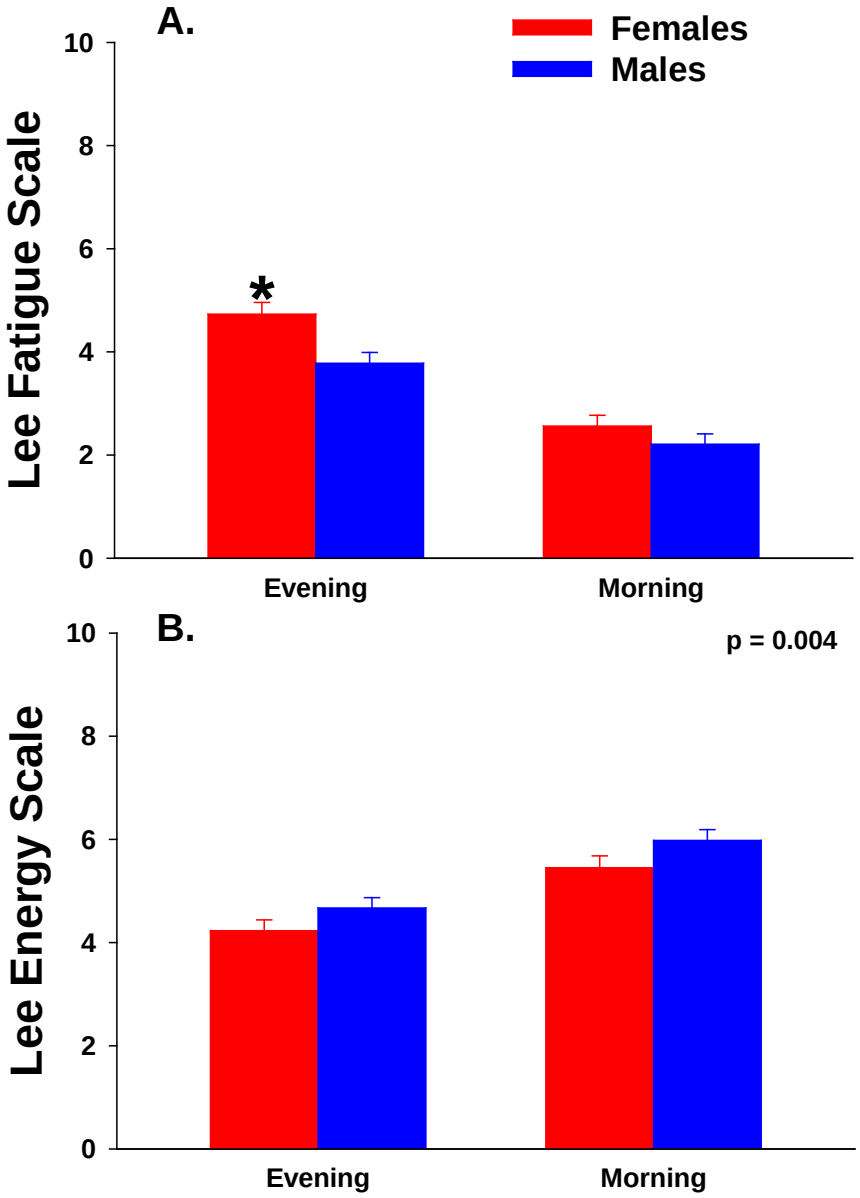
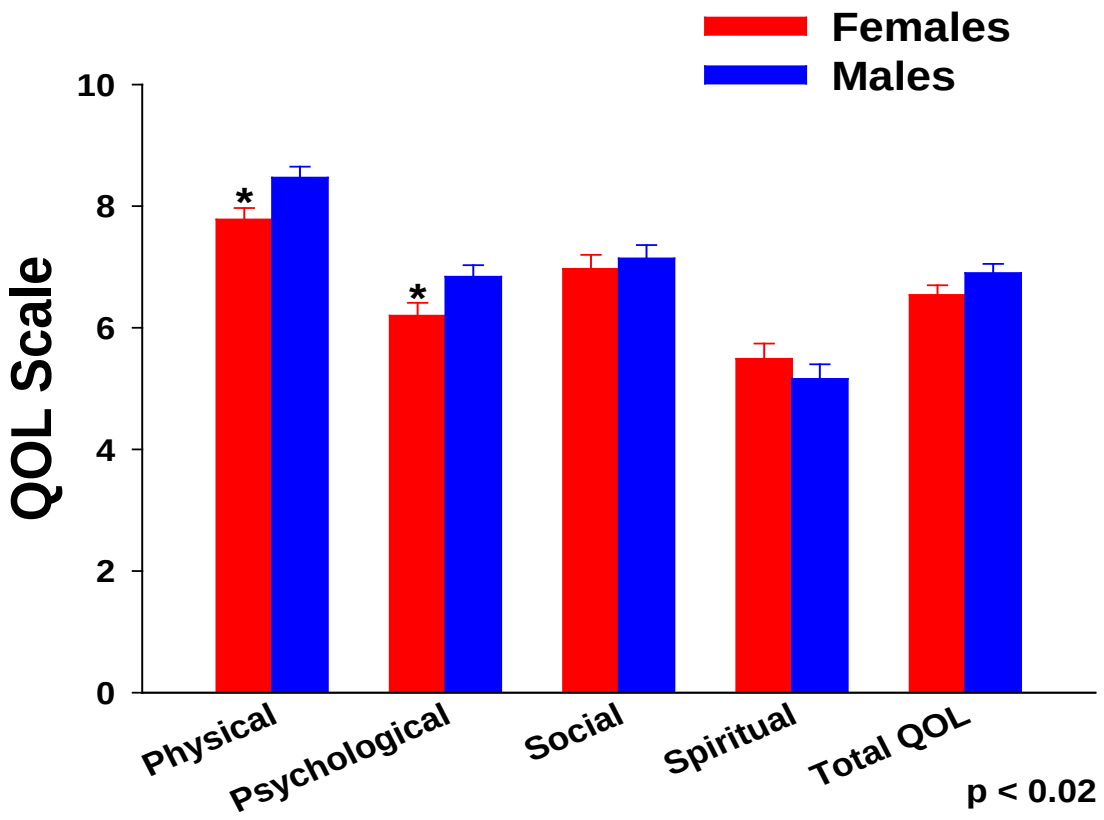


Figure 4 – Gender differences in subscale and total scores of the Quality of Life Scale – Patient Version. All values are plotted as means ± standard errors of the mean.



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