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Trajectories of Evening Fatigue in Oncology Outpatients Receiving Chemotherapy

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Abstract

Context—Fatigue is a distressing, persistent sense of physical tiredness that is not proportional to a person's recent activity. Fatigue impacts patients' treatment decisions and can limit their self-care activities. While significant interindividual variability in fatigue severity has been noted, little is known about predictors of interindividual variability in initial levels and trajectories of evening fatigue severity in oncology patients receiving chemotherapy (CTX).

Objectives—To determine whether demographic, clinical, and symptom characteristics were associated with initial levels as well as the trajectories of evening fatigue.

Methods—A sample of outpatients with breast, gastrointestinal, gynecological, and lung cancer (*N*=586) completed demographic and symptom questionnaires a total of six times over two cycles of CTX. Fatigue severity was evaluated using the Lee Fatigue Scale. Hierarchical linear modeling (HLM) was used to answer the study objectives.

Results—A large amount of interindividual variability was found in the evening fatigue trajectories. A piecewise model fit the data best. Patients who were White, diagnosed with breast,

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gynecological, or lung cancer, and who had more years of education, child care responsibilities, lower functional status, and higher levels of sleep disturbance and depression reported higher levels of evening fatigue at enrollment.

Conclusion—This study identified both non-modifiable (e.g., ethnicity) and modifiable (e.g., child care responsibilities, depressive symptoms, sleep disturbance) risk factors for more severe evening fatigue. Using this information, clinicians can identify patients at higher risk for more severe evening fatigue, provide individualized patient education, and tailor interventions to address the modifiable risk factors.

Keywords

evening fatigue; chemotherapy; hierarchical linear modeling; symptom trajectories; diurnal variations; symptom patterns; gastrointestinal cancer; breast cancer; gynecological cancer; lung cancer

Introduction

Fatigue is the most common symptom reported by oncology patients during treatment.[1] Over one-third of outpatients undergoing chemotherapy (CTX) experience clinically meaningful levels of fatigue.[2] Fatigue impairs patients' functional status and decreases their quality of life (QOL).[3,4] Fatigue can be so severe that it negatively impacts patients' treatment decisions and severely limits their self-care activities.[5–7]

Most of the longitudinal studies on fatigue in patients undergoing cancer treatment have evaluated for changes in fatigue severity over the past day,[8] weeks,[9,10] or before and after treatment.[11–13] A new and emerging area of research is an evaluation of diurnal variations in fatigue severity. For example, fatigue severity in healthy individuals varies over the course of the day, usually increasing in the evening.[14] In addition, differences in morning and evening fatigue were found in patients with rheumatoid arthritis, primary Sjögren's syndrome, systemic lupus erythematous[15] and chronic renal failure.[16]

Only four studies were identified that evaluated diurnal variations in fatigue in oncology patients undergoing CTX[17,18] or radiation therapy (RT).[19,20] In particular, our research team evaluated for differences in the trajectories and predictors of morning and evening fatigue in patients with breast[19] and prostate[20] cancer who underwent RT. For both morning and evening fatigue, women with breast cancer reported higher fatigue severity scores than men with prostate cancer.[19,20] Using hierarchical linear modeling (HLM), younger age and higher levels of sleep disturbance prior to RT were associated with higher levels of morning fatigue in the patients with breast cancer.[19] In contrast, these two characteristics predicted initial levels as well as changes over time in *both* morning and evening fatigue in patients with prostate cancer.[20] While depression predicted initial levels of evening fatigue in patients with breast cancer, it predicted both initial levels and the trajectories of morning fatigue in patients with prostate cancer. Finally, being employed, having children living at home, higher trait anxiety, lower body mass index (BMI), and a higher number of chronic conditions were associated with diurnal variability in fatigue in women with breast cancer but not in men with prostate cancer.

Only two studies were found that examined diurnal variations in morning and evening fatigue in oncology patients undergoing CTX.[17,18] In one study of a sample of 78 patients with gynecological (GYN) cancer,[18] fatigue was assessed three times a day at 10AM, 2PM, and 6PM for six days before and after the first three CTX cycles. Using the mean daily fatigue score, the authors reported "an intraday effect" of increasing fatigue severity throughout the course of the day.[18] While fatigue severity was assessed across three CTX cycles, the assessments were completed on the six days before through the six days after the infusion. Therefore, variability in fatigue severity in relationship to specific time points within a CTX cycle (e.g., acute effects of CTX, mid-cycle, recovery period) was not assessed. In addition, predictors of interindividual variability were not evaluated.

In the other study, that evaluated 18 patients with a variety of cancer diagnoses who underwent CTX or RT,[17] fatigue was measured hourly during the hours patients were awake for three days. The 72 hours of data were superimposed onto one 24-hour grid and plotted to determine if diurnal trends were present. Fatigue scores were significantly lower in the morning hours compared to the afternoon and evening hours. However, diurnal variations and predictors of fatigue associated with CTX were not reported.

This limited body of research suggests that the severity of fatigue in oncology patients varies over the course of the day.[17–20] However, only one study reported findings for patients undergoing CTX.[18] To date, no study has evaluated for interindividual variability in fatigue severity across specific points in the CTX administration cycle. In addition, predictors of interindividual variability in fatigue severity in patients receiving CTX were not evaluated.

Given the paucity of research on diurnal variations in and predictors of fatigue severity in oncology patients undergoing CTX, the purposes of this study, in a sample of outpatients with breast, gastrointestinal (GI), GYN, and lung cancer who were receiving two cycles of CTX, were to evaluate for variations in evening fatigue severity and to determine which demographic, clinical, and symptom characteristics predicted initial levels as well as the trajectories of evening fatigue.

Methods

Theoretical Framework

The Symptom Management Theory (SMT) provides the theoretical framework for this study.[21] The three essential concepts in the SMT are symptom experience, symptom management, and symptom outcomes. The SMT posits that symptoms are dynamic, evolve over time, and interact with antecedents that include demographic (e.g., age, sex, education, ethnicity, marital status) and clinical (e.g., cancer type and stage, type of treatment, comorbidities) characteristics. Symptom experiences frame the person's perception, evaluation, and responses to symptoms and are the beginning of the symptom management process.[21] Increased information on the fatigue experience of oncology patients undergoing CTX will assist with the development of tailored interventions to manage fatigue. Therefore, this study will evaluate associations between a number of demographic, clinical, and symptom characteristics and evening fatigue severity reported by patients during CTX.

Patients and Settings

This study is part of a larger, longitudinal study of the symptom experience of oncology outpatients receiving CTX. Eligible patients were ≥18 years of age; had a diagnosis of breast, GI, GYN, or lung cancer; had received CTX within the preceding four weeks; were scheduled to receive at least two additional cycles of CTX; were able to read, write, and understand English; and gave written informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs.

Instruments

The demographic questionnaire obtained information on age, sex, ethnicity, marital status, living arrangements, education, employment status, and exercise. Medical records were reviewed to obtain information on hemoglobin levels, BMI, cancer diagnosis, stage of disease, metastatic sites, and CTX cycle length.

The Karnofsky Performance Status (KPS) Scale is used extensively to evaluate functional status in patients with cancer and has well-established validity and reliability.[22] Patients rated their functional status on a 30 (I feel severely disabled and need to be hospitalized) to 100 (I feel normal; I have no complaints or symptoms) rating scale.[22]

The Self-Administered Comorbidity Questionnaire (SCQ) consists of 13 common medical conditions simplified into language that can be understood without prior medical knowledge (e.g., diabetes, hypertension).[23] Patients indicated if they had the condition, if they received treatment for it, and if it limited their activities. The SQC has well-established reliability and validity.[23]

The Lee Fatigue Scale (LFS) consists of 18 items designed to assess physical fatigue and energy.[24] Each item is rated on a 0 to 10 numeric rating scale (NRS). Total fatigue and energy scores were calculated as the mean of the 13 fatigue items and the five energy items, respectively. Higher scores indicate greater fatigue severity and higher levels of energy. Using separate LFS questionnaires, patients were asked to rate each item, based on how they felt within 30 minutes of awakening (i.e., morning fatigue and morning energy) and prior to going to bed (i.e., evening fatigue and evening energy). The LFS has established cut-off scores for clinically meaningful levels of fatigue (≥3.2 for morning fatigue, ≥5.6 for evening fatigue)[20] and energy (≥6.2 for morning energy, ≥3.5 for evening energy).[25] It was chosen for this study because it is relatively short, easy to administer, and has well-established validity and reliability.[20] In the current study, the Cronbach's alphas were 0.95 for both evening and morning fatigue, 0.93 for evening energy and 0.95 for morning energy.

The Spielberger State-Trait Anxiety Inventories (STAI-S and STAI-T) each have 20 items that are rated on a 1 to 4 scale.[26] The summed scores for each scale can range from 20 to 80, with higher scores indicating greater anxiety. The STAI-S measures a person's temporary anxiety response to a specific situation or how anxious or tense a person is "right now" in a specific situation. The STAI-T measures a person's predisposition to anxiety as part of one's personality. The STAI-S and STAI-T have well-established validity and reliability.[26] In the current study, the Cronbach's alphas were 0.96 for the STAI-S and 0.92 for the STAI-T.

The Center for Epidemiologic Studies-Depression Scale (CES-D) comprises 20 items selected to represent the major symptoms of depression.[27] Scores can range from 0 to 60, with scores ≥16 indicating the need for patients to seek a clinical evaluation for depression. The CES-D has well-established concurrent and construct validity.[27] In the current study, its Cronbach's alpha was 0.89.

The General Sleep Disturbance Scale (GSDS) consists of 21 items that assess sleep disturbance in the past week.[28] The GSDS total score is the sum of 21 items that can range from 0 (no disturbance) to 147 (extreme sleep disturbance). A total score of ≥43 indicates a clinically meaningful level of sleep disturbance. The GSDS has well-established validity and reliability in shift workers, pregnant women, and patients with cancer and HIV.[28–31] In the current study, its Cronbach's alpha was 0.83.

Study Procedures

The study was approved by the Institutional Review Board at each of the study sites. Eligible patients were approached in the infusion unit by a member of the research team to discuss participation in the study. Written informed consent was obtained from all patients. Depending on the length of their CTX cycles (i.e., 14-day, 21-day, or 28-day), patients completed study questionnaires in their homes, a total of six times over two cycles of CTX (prior to CTX administration [i.e., recovery from previous CTX cycle], approximately one week after CTX administration [i.e., acute symptoms], and approximately two weeks after CTX administration [i.e., potential nadir]).

Statistical Analyses

Descriptive statistics and frequency distributions were generated on the sample characteristics and symptom severity scores at enrollment using the Statistical Package for the Social Sciences (SPSS) v. 22.[32]

HLM based on full maximum likelihood estimation was performed in two stages using software developed by Raudenbush and Bryk.[33] The HLM methods are described in detail elsewhere.[19,20,34–36] In brief, during stage 1, intraindividual variability in evening fatigue over time was examined. A piecewise model strategy was employed to evaluate the pattern of change in evening fatigue over time because the six assessments encompassed two cycles of CTX. The six assessments were coded into two pieces. Assessments 1, 2, and 3 comprised the first piece (PW1) that was used to model change over time during the first CTX cycle. Assessments 4, 5, and 6 comprised the second piece (PW2) that was used to model change over time during the second CTX cycle. A piecewise model can be more sensitive to the timing and sequencing of changes in a dependent variable than conventional HLM models that would have assessed linear, quadratic, or cubic changes over the six assessments and would not have paid attention to the two different CTX cycles.[37]

The second stage of the HLM analysis examined interindividual differences in the piecewise trajectories of evening fatigue by modeling the individual change parameters (i.e., intercept and slope parameters) as a function of proposed predictors at level 2. Table 1 lists the potential predictors that were developed based on a review of the literature on fatigue in oncology patients undergoing CTX.

To improve estimation efficiency and construct a parsimonious model, exploratory level 2 analyses were completed in which each potential predictor was assessed to determine whether it would result in a better fitting model if it alone were added as a level 2 predictor. Predictors with a *t* value of <2.0 were excluded from subsequent model testing. All potential significant predictors from the exploratory analyses were entered into the model to predict each individual change parameter. Only predictors that maintained a statistically significant contribution in conjunction with other predictors were retained in the final model. A *P*-value of <0.05 indicated statistical significance.

Results

Sample Characteristics

The demographic, clinical, and symptom characteristics of the sample (*N*=586) are presented in Table 2. The sample was predominately female (80%, *n*=469), with a mean age of 57.2±11.9 years, was well educated (16.3±3.0 years), currently not working for pay (66%, *n*=385), partnered (68%, *n*=397), and did not have child care responsibilities (77% *n*=452). On average, the patients were 2.5±4.4 (median = 0.49) years from their cancer diagnosis, primarily being treated with 21-day CTX cycles (55%), and with one metastatic site. At enrollment, the mean scores on the GSDS and the STAI-S were above the cut-off scores for clinically meaningful levels for sleep disturbance and state anxiety, respectively.

Changes in Evening Fatigue Severity Over Time

The first HLM analysis examined how evening fatigue scores changed within the two cycles of CTX. A linear trend within each of the two CTX cycles was not significant. A quadratic trend within each of the CTX cycles was significant (*P*<.001).

The estimates for the initial piecewise model are presented in Table 3. Because the model was unconditional (i.e., no covariates), the intercept represents the average evening fatigue severity score at enrollment (i.e., 5.330 on a scale of 0 to 10). The estimated linear piecewise rates of change were 0.601 (*P*<0.0001) and 0.366 (*P*<0.0001) for piecewise linear 1 and piecewise linear 2, respectively. The estimated quadratic piecewise rates of change were −0.310 (*P*<0.0001) and −0.104 (*P*<0.0001) for piecewise quadratic 1 and piecewise quadratic 2, respectively. The combination of each coefficient determines the curves for the two piecewise components' changes in evening fatigue scores over time.

Fig. 1A displays the mean evening fatigue scores over two cycles of CTX. Evening fatigue severity rose and declined with a distinct peak at assessment 2 and a broader peak from assessment 4 to assessment 5. The results indicate a sample-wide change in evening fatigue severity over time. However, they do not indicate that all of the patients' evening fatigue severity scores changed at the same rate over time. The variance components (Table 3) suggest that considerable interindividual variability existed in the trajectories of evening fatigue. A spaghetti plot of a random 30% of the sample's data demonstrates the interindividual variability in evening fatigue (Fig. 1B). These results supported additional analyses of predictors of interindividual differences in initial levels as well as in the trajectories of evening fatigue severity.

Interindividual Differences in Initial Levels and Trajectories of Evening Fatigue

As shown in the final model (Table 3), the demographic characteristics that predicted interindividual differences in the initial levels (i.e., intercept) of evening fatigue were ethnicity education, and having children at home. The clinical characteristics that predicted interindividual differences in the initial levels of evening fatigue were functional status and cancer diagnosis. The severity of depressive symptoms and sleep disturbance at enrollment were the symptom characteristics that predicted interindividual differences in the intercept for evening fatigue.

To illustrate the effects of the various demographic, clinical, and symptom characteristics, Figs. 2A–2E display the adjusted change curves for evening fatigue that were estimated based on differences in ethnicity (i.e., ethnicity identified as White or non-White), education (i.e., less education/more education calculated as one standard deviation (SD) above and below the mean), having children at home (i.e., yes or no), functional status (i.e., lower KPS/higher KPS calculated as one SD above and below the mean KPS score), and cancer diagnosis (i.e., breast, GYN, or lung cancer versus GI). Figs. 3A and 3B display the adjusted change curves for evening fatigue that were estimated based on the differences in depressive symptoms (i.e., lower CES-D/higher CES-D calculated as one SD above and below the mean CES-D score) and sleep disturbances (i.e., lower GSDS/higher GSDS calculated as one SD above and below the mean GSDS score).

When the evening fatigue score at enrollment was added to the model as a predictor of changes in evening fatigue over time (i.e., slope) in PW1, the overall model fit improved (P=0.02) from when it was not included in the model. However the contribution of this predictor was not significant for the linear component of PW1 (P=0.15) or for the quadratic component of PW1 (P=0.45). In Fig. 3C, the modest effects of the evening fatigue score at enrollment (lower fatigue/higher fatigue calculated as one SD above the mean evening LFS score) are plotted.

Discussion

This study is the first to evaluate for and determine predictors of interindividual variability in evening fatigue severity in oncology patients undergoing two cycles of CTX. While evening fatigue scores prior to the next dose of CTX (i.e., 5.3) were just below the clinically meaningful cut-off score of 5.6,[20] substantial interindividual variability was found in these scores (Fig. 1B). In addition, using piecewise modeling, cyclic variations in evening fatigue severity were identified (i.e., during each cycle, the severity of evening fatigue increased following the administration of CTX and then decreased in the week following CTX). Taken together, these findings suggest that any evaluation of changes in evening fatigue severity over the course of multiple cycles of CTX warrant the use of more sophisticated statistical techniques like HLM.

A direct comparison of the trajectories of evening fatigue over two cycles of CTX is not possible because no other studies were identified that used the same assessment time points and HLM as the analysis method. However, the piecewise model of changes over time in evening fatigue associated with CTX administration contrasts with our previous findings

regarding changes in evening fatigue in patients with breast[19] and prostate[20] cancer who underwent RT. For both groups of patients, evening fatigue scores increased gradually from the beginning to the end of RT and then returned to pre-treatment levels at six months after the completion of RT (i.e., quadratic model). These between-treatment differences in the trajectories of evening fatigue warrant additional investigation. Because patients in the current study were not enrolled prior to their first dose of CTX and followed to the completion of treatment and post-treatment, one cannot determine if the severity of evening fatigue increased over each cycle of CTX or when these scores returned to pre-treatment levels. Detailed characterization of the trajectories of evening fatigue during and following various cancer treatments would provide valuable information that could be used to guide the timing of interventions to treat evening fatigue.

In terms of fatigue severity, no studies were identified that reported evening fatigue scores for patients undergoing CTX. However, compared to our previous work in patients undergoing RT, the mean evening fatigue score prior to CTX administration (i.e., 5.3) was higher than those reported by patients with breast (i.e., 4.9) and prostate (i.e., 3.5) cancer prior to and at the completion of RT.[19,20] While previous studies reported higher fatigue in patients who received CTX prior to RT,[38] these studies did not differentiate between evening and morning fatigue severity at different points in the course of each treatment (e.g., initiation, completion, and post-treatment follow-up). Again, additional studies that compare the severity of evening fatigue before, during, and after various cancer treatments are warranted to inform our understanding of the time course and to improve interventions to treat fatigue.

The HLM analysis provided insights into the demographic, clinical, and symptom characteristics associated with more severe evening fatigue. In terms of demographic characteristics, patients who were White reported higher levels of evening fatigue prior to their next dose of CTX (Fig. 2A). Conclusions about ethnic differences in fatigue severity cannot be drawn because prior studies reported either no differences,[9,10,39–41] or higher levels of fatigue in Black patients.[42] Of note in previous studies of patients receiving CTX where no differences in fatigue severity were found,[9,10,39–41] 90% of the patients were White. The underrepresentation of ethnic minorities in these studies may have limited the power to detect differences in fatigue severity in these patient populations.

In this study, patients who had completed more years of education (Fig. 2B) reported higher levels of evening fatigue prior to their next dose of CTX. In prior studies that examined the association between education and mean daily fatigue scores, the results are inconsistent with reports of no association,[19,20,43] positive correlations,[44] or negative correlations.[45] In a separate analysis of this study's sample, our research team examined the co-occurrence of multiple symptoms and found that patients with more years of education experienced fewer symptoms.[46] Further research would help to clarify the association between education and evening fatigue severity.

Another demographic characteristic that predicted higher levels of evening fatigue at enrollment was caring for children at home (Fig. 2C). Prior to the next dose of CTX, patients with child care responsibilities reported mean evening fatigue scores of 5.65 compared to

5.23 for patients without child care responsibilities. This same association was found in our study of women with breast cancer undergoing RT.[19] While age and race are not modifiable risk factors for higher levels of evening fatigue, child care responsibilities can be modified. Assessing patients' specific child care responsibilities and providing resources that decrease these responsibilities is an intervention that may decrease the severity of evening fatigue.

Patients' functional status (Fig. 2D) and cancer diagnosis (Fig. 2E) were the two clinical characteristics that predicted evening fatigue severity scores prior to the next dose of CTX. Consistent with previous reports that evaluated mean fatigue scores,[42,44,47] lower functional status was associated with higher evening fatigue scores. Functional status was not a predictor of evening fatigue in patients with breast[19] or prostate cancer[20] who received RT. This inconsistency may be related to the higher functional status of the patients in the RT studies (i.e., KPS scores of 87.7 and 95.7, respectively) compared to patients in this study (i.e., KPS score of 80.6). While decreases in functional status may be an outcome of increased fatigue,[48] our findings suggest that patients with poorer functional status warrant careful assessments. Additional research is needed on the efficacy of interventions to reduce fatigue and/or improve functional status.

Compared to patients with GI cancer, patients with breast, GYN, and lung cancer reported higher evening fatigue scores prior to the next dose of CTX. In prior studies of patients with mixed cancer diagnoses and treatments,[42,47,49] patients with lung cancer reported the highest levels of fatigue severity. An explanation for these differences in evening fatigue scores between GI cancer and the other cancer diagnoses is not readily apparent. While the time between doses of CTX varies among the cancer diagnoses (e.g., 14 days versus 21 days), this treatment characteristic was not a predictor of evening fatigue severity. Because of the heterogeneity in CTX regimens within and across the four cancer diagnoses, it is not possible to evaluate each regimen as a predictor of evening fatigue severity. One potential explanation, that requires further study, may be that the underlying mechanisms for diurnal variability in fatigue contribute to differences in evening fatigue severity among the diagnostic groups. A better understanding of the underlying mechanisms and the molecular characteristics associated with evening fatigue may provide some insights into the differences in fatigue severity by diagnosis.

Consistent with prior studies that reported mean fatigue scores, both depression[10,42,50–52] (Fig. 3A) and sleep disturbance[1,12,39,53,54] (Fig. 3B) were associated with higher severity of evening fatigue. In our previous HLM studies, depression was associated with higher levels of evening fatigue prior to the initiation of RT in patients with breast cancer,[19] but not in patients with prostate cancer.[20] Compared to the patients with prostate cancer (i.e., CES-D score of 5.9),[20] patients in this study (i.e., CES-D score of 12.6) had similar depressive symptom scores to the patients with breast cancer (i.e., CES-D score of 12.0). This finding suggests that evening fatigue severity varies based on the level of depressive symptoms. Support for this hypothesis is based on an examination of the predicted values of evening fatigue severity that are illustrated in Fig. 3A. The mean CES-D score at enrollment was 12.6±9.4). A patient with a CES-D score of one SD above the mean CES-D score of the current sample (i.e., 22.0) would have a predicted evening LFS score of 5.6 as compared to a predicted score of 5.1 for patients with a CES-D score one SD below the mean (i.e., 3.2).

While this difference appears to be small, patients with higher levels of depressive symptoms had clinically meaningful levels of evening fatigue prior to the next dose of CTX, based on the cut point of 5.6 for the LFS.[20] While it is possible that some collinearity exists between depressive symptoms and fatigue, the items on the LFS focus on an evaluation of physical fatigue independent of depressive symptoms.

Consistent with this study's results, the severity of sleep disturbance predicted initial levels of evening fatigue in patients with prostate cancer undergoing RT.[20] However, sleep disturbance was not a predictor of evening fatigue in patients with breast cancer who underwent RT.[19] One potential explanation for these inconsistent results is that in patients with breast cancer, other characteristics (e.g., child care responsibilities) or differences in the type of sleep disturbance (e.g., the number of nighttime awakenings) were more strongly associated with interindividual differences in evening fatigue severity.[55] Nonetheless, this finding suggests that evening fatigue severity is associated with a patient's level of sleep disturbance. Support for this hypothesis is based on an examination of the predicted values of evening fatigue severity that are illustrated in Fig. 3B. The mean GSDS score at enrollment was 52.2±19.4. A patient with a GSDS score of one SD above the mean GSDS score of the current sample (i.e., 71.6, which is above the clinically meaningful GSDS cut-off score of ≥43) would have a predicted evening LFS score of 5.84 as compared to a predicted score of 4.81 for patients with a GSDS score one SD below the mean (i.e., 32.8).

It is important to note that on average, patients in this study had clinically meaningful initial levels of sleep disturbance (i.e., GSDS scores of 52.2) at enrollment compared to the patients with prostate (GSDS scores of 33.4)[20] and breast cancer (GSDS score of 44.7)[19] at the initiation of RT. In the patients with breast and prostate cancer, evening fatigue was assessed before the initiation of RT, compared to this sample that was assessed at various points in their CTX treatment. The differences in sleep disturbance scores between CTX and RT may relate to the timing of the symptom assessments in relation to the patients' treatment (beginning versus the middle of a course of treatment); the other side effects associated with the treatment (e.g., urinary frequency associated with RT in patients with prostate cancer); or the biological effects of different treatments (e.g., systemic effects of CTX versus more localized effects of RT).

While consistent with prior reports,[4,46,56] a surprising finding from this study is that the majority of the clinical characteristics (i.e., the number of prior cancer treatments, CTX cycle length, metastatic involvement, BMI, hemoglobin levels) were not associated with enrollment levels of or the trajectories of evening fatigue. In this study, given the large sample size that is representative of the oncology population, CTX cycle lengths, and the extent of metastatic disease, alternative explanations are plausible. One potential reason why clinical characteristics were not associated with evening fatigue is that in addition to the predictors identified, interindividual variability in this symptom may be associated with genetic and epigenetic determinants. This hypothesis is supported by work from our research team[34,57] and others[58–60] on the associations between molecular mechanisms and fatigue in oncology patients. Studies are underway in our laboratory to identify the molecular markers associated with interindividual variability in evening fatigue severity in patients receiving CTX.

Although previous research found that an increased number of comorbidities was associated with more severe fatigue,[47,61] in this study, neither the number nor the severity of comorbidities predicted enrollment levels or the trajectories of evening fatigue. These inconsistent findings may be explained by differences in the methods used to assess both fatigue (i.e., specific assessment of evening fatigue scores versus a mean fatigue score) and comorbidities (i.e., combined number and comorbidity severity score versus mean number of comorbidities). A more detailed assessment of the comorbidity burden (i.e., not limited to number and severity) may clarify the association between comorbidities and diurnal variability in fatigue severity.

Whereas exercise is an effective intervention for decreasing fatigue in patients with cancer (for review, see reference 62), regular exercise was not a predictor of evening fatigue severity in this study. One potential explanation for this finding may be the question that was used to evaluate regular exercise. In this study, 70.3% of the sample responded that they exercised on a regular basis. A more detailed assessment of the types and frequency of exercise may clarify whether and how exercise influences interindividual variability in the severity of evening fatigue.

Several limitations and strengths need to be acknowledged. Because patients were recruited at various points in their CTX treatment, changes in fatigue severity from the initiation of CTX cannot be evaluated. The majority of the sample had at least four years of college education, which is not representative of the U.S. population (only 27% have four years of college[63]). Patients rated their experience of evening fatigue severity over the last week. Daily assessments of evening fatigue may provide more insights into the variability of evening fatigue during a CTX cycle.[64] However, this large, representative sample of oncology outpatients undergoing CTX, the evaluation of fatigue across two cycles of CTX, and the use of HLM to identify predictors of evening fatigue are major strengths of this study.

Clinical Implications

This study identified both non-modifiable (e.g., ethnicity) and modifiable (e.g., child care responsibilities, depressive symptoms, sleep disturbance) risk factors for more severe evening fatigue. Using this information, clinicians can identify patients at higher risk for more severe evening fatigue, provide individualized patient education, and tailor interventions towards these modifiable risk factors. For example, interventions that decrease child care responsibilities (e.g., providing on-site care for the patient's pre-school age children during CTX infusions) or improve functional status (e.g., functional assessment and self-management education) may decrease evening fatigue severity. Patient education about the mid-cycle increase in evening fatigue severity may help patients and their family caregivers deal with this distressing symptom. Initial and ongoing assessments and management of depressive symptoms and sleep disturbance during CTX treatment may decrease evening fatigue severity. Knowledge of these modifiable risk factors, as well as the cyclic variations in evening fatigue severity, will assist clinicians to identify and treat patients at highest risk for evening fatigue.

Future Research

Because this study is the first to characterize diurnal variations and predictors of evening fatigue during CTX, additional research is warranted to confirm these findings. Future studies need to evaluate patients at the initiation of CTX and follow them through and after the completion of treatment. In addition, the underlying mechanisms of fatigue and especially diurnal variability in fatigue require further investigation. Research is needed that identifies the molecular markers that place patients at higher risk for increases in evening fatigue severity. All of these studies would provide needed information to support the development and testing of interventions to decrease fatigue. In our companion paper,[65] information is provided on the trajectories and predictors of morning fatigue that will fill an important gap on diurnal variability in fatigue severity.

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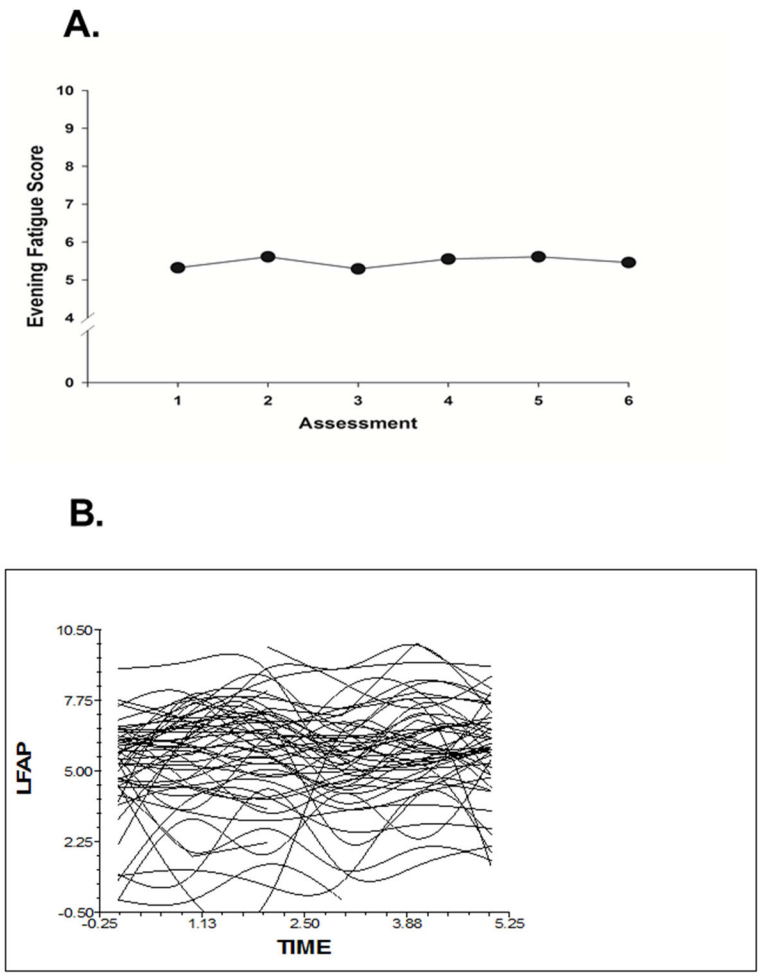

Fig. 1.

Fig. 1A. Piecewise model of mean evening fatigue scores for six assessment points over two cycles of chemotherapy (CTX).

Fig. 1B. Spaghetti plots of individual evening fatigue trajectories for a random sample of 30% of the total sample (n=175) over two cycles of CTX. LFAP = Lee Fatigue Scale Evening severity score.

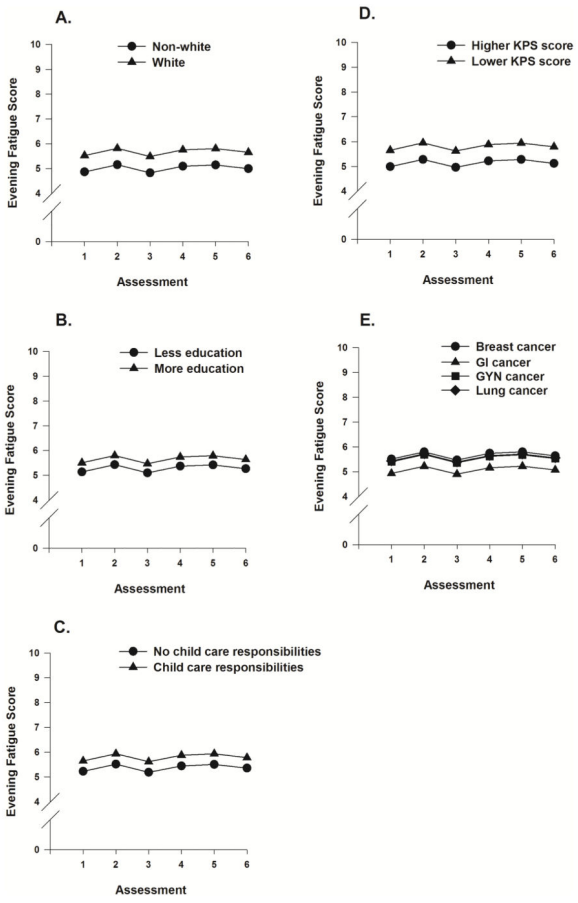

Fig. 2.

Figs. 2A–E. The adjusted change curves for evening fatigue that were estimated based on differences in ethnicity (i.e., ethnicity identified as White or non-White), education (i.e., less education/more education calculated as one standard deviation (SD) above and below the mean), having children at home (i.e., yes or no), functional status (i.e., lower Karnofsky Performance Status (KPS) score/higher KPS score calculated as one SD above and below the mean KPS score), and cancer diagnosis (breast, GYN, or lung cancer versus GI).

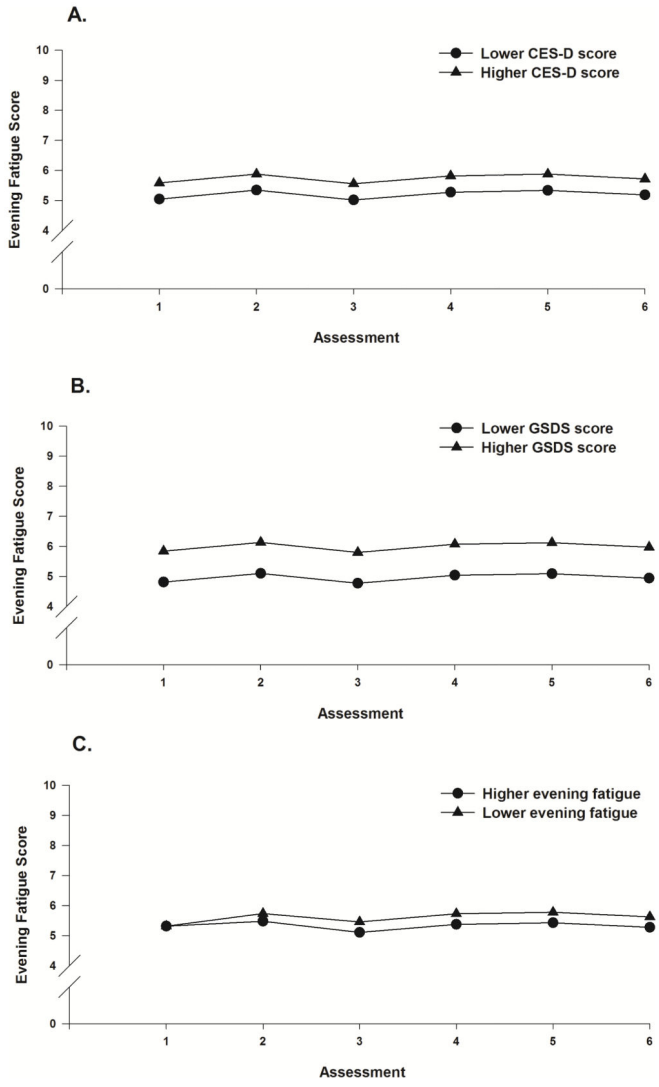

Fig. 3.

Figs. 3A–C. Figs. 3A and 3B display the adjusted change curves for evening fatigue that were estimated based on the differences in depressive symptoms (lower Center for Epidemiological Studies-Depression (CES-D) score/higher CES-D score calculated as one standard deviation (SD) above and below the mean CES-D score) and sleep disturbances (lower General Sleep Disturbance Scale (GSDS) score/higher GSDS calculated as one SD above and below the mean GSDS score). In Fig. 3C, the modest effects of the evening fatigue score at enrollment (lower fatigue/higher fatigue calculated as one SD above the mean evening Lee Fatigue Scale score) are plotted.

Table 1

Potential Predictors of Intercept, and Piecewise 1 and Piecewise 2 Linear and Quadratic Components for Evening Fatigue

Potential Predictors	Intercept	Piecewise 1 Linear Component	Piecewise 1 Quadratic Component	Piecewise 2 Linear Component	Piecewise 2 Quadratic Component
Demographic Characteristics					
Age	◆				
Sex	◆				
Ethnicity (White versus Non-White)	◆				
Education	◆				
Marital status					
Live alones					
Employment status					
Child care responsibilities	◆				
Clinical Characteristics					
Body mass index (kg/m^2)					
Hemoglobin (gm/dL)					
Karnofsky Performance Status Scale score	◆				
Self-administered Comorbidity Questionnaire score	◆				
Exercise on a regular basis					
Cancer diagnosis (breast, gastrointestinal, gynecological, lung)	◆				
Time since cancer diagnosis					
Any prior cancer treatments	◆				
Number prior cancer treatments					
Type of prior cancer treatments					
Chemotherapy cycle length	◆				
Number of metastatic sites including lymph node involvement			◆		◆
Number of metastatic sites excluding lymph node involvement					
Symptom Characteristics					
Lee Fatigue Scale: Evening fatigue score at enrollment	◆		◆		
Lee Fatigue Scale: Morning fatigue score at enrollment	◆	◆	◆		
Lee Fatigue Scale: Evening energy score at enrollment	◆				
Lee Fatigue Scale: Morning energy score at enrollment					

Potential Predictors	Intercept	Piecewise 1 Linear Component	Piecewise 1 Quadratic Component	Piecewise 2 Linear Component	Piecewise 2 Quadratic Component
Center for Epidemiological Studies-Depression Scale score at enrollment	◆				
General Sleep Disturbance Scale score at enrollment	◆				
Trait Anxiety score at enrollment	◆				
State Anxiety score at enrollment	◆				
Pain present at enrollment	◆				

◆From exploratory analysis had a *t*-value of ≥ 2.0.

Abbreviations: gm/dL = grams per deciliter; kg/m^2 = kilogram per meters squared.

Table 2

Demographic, Clinical, and Symptom Characteristics of the Patients (n=586)

Demographic Characteristics	
Age (years; mean (SD))	57.2 (11.9)
Gender (% female (n))	80.0 (469)
Ethnicity (% (n))	
White	69.3 (406)
Black	7.0 (41)
Asian/Pacific Islander	12.8 (75)
Hispanic/Mixed/Other	10.9 (64)
Education (years; mean (SD))	16.3 (3.0)
Married or partnered (% yes (n))	67.7 (397)
Lives alone (% yes (n))	19.8 (116)
Currently employed (% yes (n))	34.3 (201)
Child care responsibilities (% yes (n))	22.9 (134)
Income (% yes (n))	
Less than $30,000	18.7 (98)
$30,000 to <$70,000	17.8 (104)
$70,000 to < $100,000	15.2 (89)
More than $100,000	39.9 (234)
Clinical Characteristics	
Self-administered Comorbidity Questionnaire score (mean (SD))	5.6 (3.0)
Body mass index (kg/m^2; mean (SD))	26.3 (5.8)
Hemoglobin (gm/dL; mean (SD))	11.7 (1.4)
Karnofsky Performance Status score (mean (SD))	80.6 (11.8)
Exercise on a regular basis (% yes (n))	70.5 (413)
Specific comorbidities reported (% yes (n))	
High blood pressure	31.4 (184)
Back pain	27.0 (158)
Depression	20.5 (120)
Osteoarthritis	13.7 (80)
Anemia or blood disease	12.1 (71)
Lung disease	9.9 (58)
Diabetes	8.7 (51)
Liver disease	6.8 (40)
Heart disease	5.5 (32)
Rheumatoid arthritis	4.1 (24)
Ulcer or stomach disease	4.1 (24)
Kidney disease	1.2 (7)
Cancer diagnosis (% yes (n))	
Breast	42.8 (251)
Gastrointestinal	26.8 (157)

Gynecological	20.3 (119)
Lung	10.1 (59)
Time since cancer diagnosis (years; mean (SD))	2.5 (4.4)
Time since cancer diagnosis (years; median)	0.49
Any prior cancer treatments (% yes (n))	82.4 (483)
Number prior cancer treatments (mean (SD))	1.9 (1.6)
Type of prior cancer treatment (% yes (n))	
No prior treatment	17.6 (103)
Only surgery, chemotherapy, or RT	40.4 (237)
Surgery and chemotherapy, or surgery and RT, or chemotherapy and RT	23.0 (135)
Surgery and chemotherapy and RT	17.7 (104)
Chemotherapy cycle length (% (n))	
14 days	36.0 (211)
21 days	55.3 (324)
28 days	8.7 (51)
Number of metastatic sites including lymph node involvement (mean (SD))	1.4 (1.3)
Number of metastatic sites excluding lymph node involvement (mean (SD))	0.9 (1.2)
Symptom Characteristics at Enrollment	
Lee Fatigue Scale: evening fatigue score (mean (SD))	5.3 (2.1)
Lee Fatigue Scale: morning fatigue score (mean (SD))	3.1 (2.2)
Lee Fatigue Scale: evening energy score (mean (SD))	3.5 (1.9)
Lee Fatigue Scale: morning energy score (mean (SD))	4.5 (2.2)
Center for Epidemiological Studies-Depression Scale score (mean (SD))	12.6 (9.4)
General Sleep Disturbance Scale score (mean (SD))	52.2 (19.4)
Trait Anxiety score (mean (SD))	35.0 (10.4)
State Anxiety score (mean (SD))	33.2 (12.1)
Pain present (% yes (n))	73.5 (431)

Abbreviations: gm/dL = grams per deciliter; kg/m^2 = kilograms per meters squared; SD = standard deviation; RT = radiation therapy.

Table 3

Hierarchical Linear Model for Evening Fatigue

Evening Fatigue	Coefficient (SE)	
	Unconditional Model	Final Model
Fixed effects		
Intercept	5.330 (.087)$^{+}$	5.324 (.080)$^{+}$
Piecewise 1 – linear rate of change	0.601 (.132)$^{+}$	0.600 (.130)$^{+}$
Piecewise 1 – quadratic rate of change	−0.310 (.064)$^{+}$	−0.309 (.063)$^{+}$
Piecewise 2 – linear rate of change	0.366 (.085)$^{+}$	0.369 (.084)$^{+}$
Piecewise 2 – quadratic rate of change	−0.104 (.027)$^{+}$	−0.104 (.027)$^{+}$
Time invariant covariates		
Intercept		
Non-White		−0.658 (.149)$^{+}$
Education		0.062 (.023)*
Child care responsibilities		0.426 (.162)*
Functional status		−0.028 (.006)$^{+}$
Diagnosis[a]		
Breast cancer versus GI cancer		0.577 (.165)$^{+}$
GYN cancer versus GI cancer		0.462 (.197)*
Lung cancer versus GI cancer		0.491 (.250)*
Depressive symptoms		0.029 (.009)**
Sleep disturbance		0.027 (.004)$^{+}$
Piecewise 1 – linear rate of change		
Evening fatigue at enrollment		−0.084 (.059)
Piecewise 1 – quadratic rate of change		
Evening fatigue at enrollment		0.021 (.028)
Variance components		
In intercept	1.697^{+}	1.510^{+}
Goodness-of-fit deviance (parameters estimated)	11231.397 (7)**	11034.988096 (18)*
Model comparison χ^2 (df)		196.409 (11)$^{+}$

[a] Diagnosis – represented by three “dummy” coded variables significantly improved the model fit (p=.004)

* p<.05,

** p<.001,

$^{+}$ p<.0001

Abbreviations: df = degrees of freedom; GI = gastrointestinal cancer; GYN = gynecological cancer; SE = standard error