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Trajectories of Fatigue in Family Caregivers of Patients Undergoing Radiation Therapy for Prostate Cancer

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Abstract

Predictors of and trajectories for evening and morning fatigue were evaluated in family caregivers of oncology patients using hierarchical linear modeling. Evening fatigue trajectory fit a quadratic model. Predictors included baseline sleep disturbances in family caregivers and baseline evening fatigue in patients. Morning fatigue trajectory fit a linear model. Predictors were baseline trait anxiety, levels of perceived family support, and baseline morning fatigue in patients. Findings suggest considerable inter-individual variability in the trajectories of evening and morning fatigue. Evaluating family caregivers for sleep disturbance, anxiety, and poor family support, as well as high levels of patient fatigue, could identify those family caregivers at highest risk for sustained fatigue trajectories.

Keywords

fatigue; trajectories; family caregivers; radiation therapy; prostate cancer; hierarchical linear modeling

In the last decade, the number of family caregivers (FCs) caring for a patient with cancer has grown, and the complexity of that care has greatly increased. With cancer treatment now routinely delivered in the outpatient setting, much of the care and support that patients need is provided at home by FCs (B. A. Given, Given, & Kozachik, 2001). Care may range from emotional support to round-the-clock symptom management, complex technical care, frequent medical appointments, and travel (B. A. Given & Given, 1994; Weitzner, Haley, & Chen, 2000). These activities may consume a considerable portion of the FC's day and may last for months (Nijboer et al., 1998). Caregiving may be added to an already full schedule that includes employment, household management, and meeting the needs of other family members. In addition, emotional distress associated with the cancer diagnosis may add to the

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burden that FCs experience (Blanchard, Albrecht, & Ruckdeschel, 1997; B. Given et al., 2006; Pitceathly & Maguire, 2003).

Given these demands, fatigue among FCs is a growing health concern. Higher levels of FC fatigue are associated with decreased functional status and poorer quality of life (QOL; Cho, Dodd, Lee, Padilla, & Slaughter, 2006; Fletcher et al., 2008). Sustained fatigue may pose health and safety risks for FCs, and a fatigued FC may be less able to assimilate new information needed for caregiving. However, little is known about predictors of high levels of fatigue and even less is known about changes in fatigue across the course of cancer treatment. Therefore, the purpose of this longitudinal study was to examine predictors and trajectories of fatigue in FCs of patients undergoing radiation therapy (RT) for prostate cancer.

The University of California, San Francisco Symptom Management Model (SMM) was the conceptual framework for this study. The SMM is a multidimensional model that includes three dimensions of symptoms (experience, management, and outcomes) and the three domains of nursing (person, environment, and health/illness; Dodd et al., 2001; Larson et al., 1994). This study focused on the fatigue experience and selected predictors from each nursing domain.

The Fatigue Experience

The fatigue experience of FCs of oncology patients has been investigated primarily in terms of fatigue severity. Evidence from multiple studies suggests that on average, FCs experience low to moderate levels of fatigue (Campbell et al., 2004; Campbell et al., 2007; Cho et al., 2006; Ferrell, Grant, Borneman, Juarez, & ter Veer, 1999; Fletcher et al., 2008; Gaston-Johansson, Lachica, Fall-Dickson, & Kennedy, 2004; S. Jensen & Given, 1991; Miaskowski, Kragness, Dibble, & Wallhagen, 1997; Passik & Kirsh, 2005; Schumacher et al., 2008). However, considerable variability in fatigue was found in virtually every study, and some investigators reported extremely high fatigue scores (Gaston-Johansson et al.; Schumacher et al.).

Diurnal variation is an aspect of the fatigue experience that has received little attention in family caregiving research, although it has been investigated in oncology patients (Curran, Beacham, & Andrykowski, 2004; Glaus, 1993) and in other populations (Cahill, 1999; Lee, 2001; Sonnenschein, Sorbi, van Doornen, Schaufeli, & Maas, 2007). In an earlier analysis, we examined both evening and morning fatigue in FCs at the initiation of RT for prostate cancer patients, and reported the prevalence of clinically significant levels of both (Fletcher et al., 2008). Clinical significance was determined using published cutpoints for scores on the Lee Fatigue Scale (5.6 for evening fatigue and 3.2 for morning fatigue on a scale ranging from 0–10; Chang et al., 2007; Lee, Hicks, & Nino-Murcia, 1991; Mendoza et al., 1999). Thirty percent of FCs reported clinically significant levels of evening fatigue, and 33.3% reported clinically significant levels of morning fatigue. Mean evening fatigue scores (4.3 ± 2.3) were significantly higher than those for morning fatigue (2.6 ± 2.1 , $p \leq .001$). Recently, several authors suggested that evaluation of diurnal variations in fatigue severity might provide insights into the specific etiologies of fatigue (Curran et al.; Dimsdale, Ancoli-Israel, Ayalon, Elsmore, & Gruen, 2007; Hacker & Ferrans, 2007).

Family caregiver fatigue over time is another aspect of the fatigue experience that has received little research attention. To our knowledge, change in fatigue over time in FCs of oncology patients has been evaluated in only one study. Passik and Kirsh (2005) reported a small decrease in fatigue over a period of 30 days.

Nursing Domains as Predictors of Fatigue

Although fatigue appears to be a significant problem for FCs of oncology patients, only a few researchers have evaluated the relationships between person, environment, or health/illness predictors and FCs' level of fatigue. In the person domain, Cho et al. (2006) found that female FCs of gastric cancer patients reported higher fatigue than males. Personal characteristics that negatively correlated with fatigue included FC age (Gaston-Johansson et al., 2004; Schumacher et al., 2008), self-efficacy (Campbell et al., 2004), preparedness (Schumacher et al.), and sleep quality (Cho et al.). Findings on the association between fatigue and FCs' socioeconomic status are inconsistent. Gaston Johansson et al. reported that married FCs and those with higher socioeconomic status reported less fatigue, whereas, no relationship was found between FC fatigue and employment status in two other studies (Campbell et al. 2004; Jensen & Given, 1991).

Some evidence supports an association between FC fatigue and characteristics of the caregiving environment. Several researchers found that perceived caregiving difficulty, burden, and caregiver strain were associated with higher levels of fatigue (Cho et al., 2006; Gaston-Johansson et al., 2004; Passik & Kirsh, 2005; Schumacher et al., 2008). The time demands of caregiving may be associated with fatigue, although results are inconclusive. Finally, S. Jensen and Given (1991) and Passik and Kirsh found that higher levels of fatigue were associated with a greater impact of caregiving on the FC's schedule, and caregiving demands were associated with higher levels of fatigue. However, S. Jensen and Given did not find a significant association between hours of care or duration of caregiving and fatigue severity.

Health/illness predictors of FCs' fatigue have received only limited attention. Higher FC depression, anxiety, and sleep disturbance were associated with higher levels of fatigue in three studies (Cho et al., 2006; Gaston-Johansson et al., 2004; Schumacher et al., 2008). Decreased FC functional status and poorer QOL were associated with higher fatigue severity in our recent study (Fletcher et al., 2008). Only two researchers have explored patient health/illness variables as potential predictors of FC fatigue. No difference in fatigue severity was found between FCs of patients with and without pain (Miaskowski et al., 1997). Similarly, no significant relationship was found between FCs' and patients' levels of fatigue (Passik & Kirsh, 2005). However, we postulated that patients' experiences with fatigue could have an impact on their FC. For example, a patient with prostate cancer who uses the bathroom several times a night because of the side effects of RT, may disturb his bed partner and increase her fatigue.

In summary, evidence suggests that some FCs of oncology patients experience high levels of fatigue, yet little is known about what predicts fatigue severity or how fatigue changes over time. To our knowledge, no researchers have explored predictors of change in FC fatigue over time or differentiated evening from morning fatigue over time. Moreover, FCs in previous research were at different points in the cancer experience, which limits any conclusions about the relationships between FCs' level of fatigue and the patients' disease or treatment experience. To move this area of inquiry forward, researchers need to examine changes in evening and morning FC fatigue over time, beginning at a defined point in the cancer experience and covering a period of high risk for fatigue, such as a period of intensive treatment. Thus our specific aims were: (a) to examine trajectories of evening and morning fatigue from the time of the RT simulation visit (i.e., the treatment planning visit approximately 1 week prior to the start of RT) to 4 months after the completion of RT, and (b) to investigate whether selected personal, environmental, and health/illness characteristics of FCs and selected personal and health/illness characteristics of patients predicted initial levels of FC fatigue and/or trajectories of evening and morning fatigue.

Method

Design

This descriptive, longitudinal study is part of a larger investigation of multiple symptoms in patients with prostate, breast, lung, and brain cancers who underwent primary or adjuvant RT and their FCs (National Institute of Nursing Research R01 [NR04835]; Fletcher et al., 2008; Miaskowski et al., 2008).

Participants and Settings

Patients with prostate cancer were recruited through referrals from physicians and nurses at two study sites: a comprehensive cancer center and a community based hospital (Miaskowski et al., 2008). At the time of the simulation visit, patients were approached by a research nurse to discuss participation in the study. If a patient consented to the study, his FC was invited to participate.

FCs were eligible to participate if they: were ≥ 18 years of age; were able to read, write, and understand English; gave written informed consent; had a functional status score of ≥ 60 out of 100 on the Karnofsky Performance Status (KPS) scale (Karnofsky, 1977); were living with the patient who was receiving primary or adjuvant RT for prostate cancer; and did not have a diagnosed sleep disorder.

Patients were eligible if they: were ≥ 18 years of age; were able to read, write, and understand English; gave written informed consent; had a KPS score of ≥ 60 ; and were scheduled to receive primary or adjuvant RT (i.e., RT after the primary treatment). Patients were excluded if they had metastatic disease; had more than one cancer diagnosis, or had a diagnosed sleep disorder.

A total of 188 patients with prostate cancer were approached, and 82 consented to participate (43.6% response rate). The major reasons for refusal were being too overwhelmed with their cancer or too busy. Of these 82, 60 had a FC who agreed to participate. These 60 patients and their FCs constituted the sample for this analysis.

FCs were females, approximately 64 years of age and well educated; 80% were White, and approximately 37% were employed at the time of the study (Table 1). Their mean baseline KPS score was 94.0. Over 35% reported back problems, arthritis, hypertension, or headaches.

Patients were approximately 68 years of age, with mean KPS scores of 96.8 (Table 1). Most were in clinical stages T1 or T2 (Table 2). Over 50% had received hormonal therapy prior to the initiation of RT. The mean time since diagnosis was 9.7 ± 15.1 months. The mean baseline symptom severity scores for both FCs and patients are listed in Table 1. Significant differences were found between FCs and patients in baseline ratings of depression ($p=.011$), trait ($p=.009$) and state ($p=.003$) anxiety, and evening fatigue ($p=.007$).

Instruments

Fatigue severity was measured with the 13-item Lee Fatigue Scale (LFS; Lee et al., 1991). Each item was rated on a 0 to 10 numeric rating scale (NRS), and a total score was calculated as the mean of the 13 items, with higher scores indicating greater fatigue severity. Respondents were asked to rate each item based on how they felt "right now," within 30 minutes of awakening (morning fatigue), and prior to going to bed (evening fatigue). The LFS has been used with healthy individuals, (Gay, Lee, & Lee, 2004; Lee et al., 1991) and in patients with cancer and HIV (Lee, Portillo, & Miramontes, 1999; Miaskowski & Lee, 1999). It was chosen for this study because it is relatively short, easy to administer, and has

well established validity and reliability. The Cronbach's alpha for evening fatigue was .96 and for morning fatigue was .94 in patients undergoing evaluation for sleep disorders (Lee et al., 1999). In this sample of FCs and patients, Cronbach's alphas for evening and morning fatigue at baseline were .95 and .96, respectively.

Baseline sleep disturbance was measured with the 21-item General Sleep Disturbance Scale (GSDS; Lee, 1992). Each item was rated on a 0 (*never*) to 7 (*everyday*) NRS. Items are summed to yield a total score that can range from 0 (*no disturbance*) to 147 (*extreme sleep disturbance*). The GSDS has well-established validity and reliability in shift workers, pregnant women, and patients with cancer and HIV (Ahlberg, Ekman, & Gaston-Johansson, 2005; Lee, 1992; Lee & DeJoseph, 1992; Lee, Portillo, & Miramontes, 2001; Miasowski & Lee, 1999). The Cronbach's alpha in a study of women seropositive for HIV was .80 (Lee et al., 2001). In the current study, the Cronbach's alphas were .79 and .81 for FCs and patients, respectively.

Baseline level of depression was measured with the 20-item Center for Epidemiologic Studies – Depression scale (CES-D; Radloff, 1977). Scores of ≥ 16 indicate the need for individuals to seek clinical evaluation for major depression. The CES-D has well established concurrent and construct validity (Carpenter et al., 1998; Sheehan, Fifield, Reisine, & Tennen, 1995). The Cronbach's alpha for patients with cancer was .92 (Carpenter et al.). In this study, Cronbach's alphas were .84 and .83 for FCs and patients, respectively.

Baseline level of anxiety was measured with the 20-item Spielberger State Trait Anxiety Inventories (STAI-S and STAI-T; Spielberger, Gorsuch, Suchene, Vagg, & Jacobs, 1983). Higher scores indicate greater anxiety. The STAI-T measures an individual's predisposition to anxiety determined by his/her personality and estimates how a person feels generally. The STAI-S measures an individual's transitory emotional responses to a stressful situation. It evaluates the emotional responses of worry, nervousness, tension, and feelings of apprehension related to how people feel "right now" in a stressful situation. The STAI-S and STAI-T inventories have well established criterion and construct validity and internal consistency reliability coefficients. The Cronbach's alpha for the STAI ranges from .83 to .92 (Spielberger et al.). In this study, the Cronbach's alphas for the STAI-T and STAI-S for FCs were .89 and .93, respectively. The Cronbach's alphas for the STAI-T and STAI-S for patients were .86 and .91, respectively.

Baseline levels of worst pain intensity were evaluated using 0 (*no pain*) to 10 (*excruciating pain*) NRSs. A descriptive NRS is a valid and reliable measure of pain intensity (M. P. Jensen, Chen, & Brugger, 2003).

The 24-item Caregiver Reaction Assessment (CRA; Given et al., 1992) was used to measure multiple dimensions of the caregiving experience including impact on FCs' health, schedule, and finances, and self esteem for caregiving and family support (C. W. Given et al.; Nijboer, Triemstra, Tempelaar, Sanderman, & van den Bos, 1999). Items are rated on a Likert type scale that ranges from 1 (*strongly agree*) to 5 (*strongly disagree*). The CRA has well established validity and reliability in FCs of patients with cancer (C. W. Given et al.; Kurtz, Kurtz, Given, & Given, 2004; Nijboer, Tempelaar, Triemstra, van den Bos, & Sanderman, 2001; Nijboer et al., 1999; Sherwood, Given, Given, & von Eye, 2005). The Cronbachs alphas for patients with cancer was: Impact of Schedule .81, Impact on Finances .83, Lack of Family Support .62, Health and Illness .68, and Family Caregiver Self Esteem .73 (Nijboer et al., 1999). In this sample, Cronbachs alphas for the subscales at baseline ranged from .55 (Lack of Family Support) to .84 (Impact on Schedule).

A demographic questionnaire was used to obtain information on age, marital status, years of education, living arrangements, ethnicity, and employment status. In addition, patients and

FCs completed a checklist of comorbidities and self-rated their functional status on the KPS (Karnofsky, 1977). Patients' medical records were reviewed for disease and treatment information.

Procedures

The study was approved by the Human Subjects Committees at each of the sites. Following recruitment, patients were asked to identify the person most involved in their care (i.e., their FC). If the FC was present, the research nurse explained the study and obtained written informed consent from the FC. FCs who were not with the patient were contacted by telephone to determine their interest in study participation. The research nurse visited the FC's home, obtained written informed consent, and enrolled her in the study.

After obtaining written informed consent, patients and FCs completed the baseline study questionnaires. They were taught to complete the Lee Fatigue Scale (LFS; Lee et al., 1991) before going to bed each night (i.e., evening fatigue) and upon arising each morning (i.e., morning fatigue) for 2 consecutive days. Baseline assessments were done during the simulation visit (when treatment was planned but no radiation was administered), weekly during the course of RT, every 2 weeks for the first 2 months, and once a month for the next 2 months following the completion of RT. The majority of the FCs completed 16 assessments of evening and morning fatigue. Every FC provided data for at least 12 of the 16 assessments.

Data Analysis

Descriptive statistics and frequency distributions were generated on the sample characteristics using SPSS™ Version 14.0. For each of the 16 assessments that was done on 2 consecutive days, a mean evening and morning LFS score was calculated for use in the subsequent statistical analyses.

Hierarchical linear modeling (HLM), based on full maximum likelihood estimation, was done using the software developed by Raudenbush & Byrk (2002). The repeated measures of fatigue were conceptualized as being nested (or contained) within individuals. Compared with other methods of analyzing change, HLM has two major advantages. First, HLM can accommodate unbalanced designs, which allows for the analysis of data when the number and the spacing of the assessments vary across respondents. Although every FC was to be assessed on a pre-specified schedule, the actual number of assessments was not the same for all of them because some patients had longer periods of RT and some had scheduling conflicts. HLM can accommodate for these differences. Second, HLM helps to identify more complex patterns of change that are often overlooked using other methods.

With HLM, the repeated measures of the outcome variable (i.e., evening or morning fatigue in FCs) are nested within individuals, and the analysis of change in fatigue scores has two levels. In HLM terminology, Level 1 refers to change within persons (i.e., intra-individual) and Level 2 refers to change between persons (i.e., inter-individual). At Level 1, the outcome is conceptualized as varying within individuals and is a function of person-specific change parameters (i.e., intercept and linear or quadratic slopes) plus error. At Level 2, these person-specific change parameters are multivariate outcomes that vary across individuals. Level 2 outcomes were modeled as a function of personal, environmental, and health/illness characteristics that vary between individuals, plus an error associated with the individual. Combining Level 1 with Level 2 results in a mixed model with both fixed and random effects (Raudenbush & Bryk, 2002).

Separate HLM analyses were done to evaluate for changes over time in FC evening and morning fatigue. Each HLM analysis proceeded in two stages. First, intraindividual (within

individual) variability in fatigue over time was examined. Time referred to the length of time from the simulation visit to 4 months after the completion of RT (i.e., 6 months with a total of 16 assessments). Three Level 1 models were compared, representing that the FCs' fatigue severity (a) did not change over time (i.e., no time effect), (b) changed at a constant rate (i.e., linear time effect), or (c) changed at a rate that accelerated or decelerated over time (i.e., quadratic time effect). At this point, the Level 1 model was constrained to be unconditional (i.e., no predictors) and likelihood ratio tests were used to determine the best model. These analyses addressed the first specific aim and identified the change parameters that best described intra-individual changes in evening and morning fatigue severity over time.

The second stage of the HLM analysis, which addressed the second specific aim, examined inter-individual (or between individual) differences in the trajectories of evening and morning fatigue in FCs by modeling the individual change parameters (i.e., intercept and linear and quadratic slopes) as a function of proposed predictors at Level 2.

As shown in Table 3, the SMM was used as an organizing framework for the potential predictors of fatigue that were identified from the literature and clinical experience. To improve estimation efficiency and construct a model that was parsimonious, an exploratory Level 2 analysis was done in which each potential predictor was assessed to see if it would result in a better fitting model when it alone was added as a Level 2 predictor. Predictors with a *t*-value of < 2.0 were dropped from subsequent model testing. All of the potentially significant predictors from the exploratory analyses were entered into the model to predict each individual change parameter (i.e., intercept, and linear or quadratic slopes). Only predictors that maintained a significant contribution in conjunction with other variables were retained in the final model. A *p*-value of <.05 indicated statistical significance.

Results

Intra-Individual Changes in Fatigue in Family Caregivers

Intra-individual changes in evening and morning fatigue from the time of the simulation visit to 4 months after the completion of RT were examined as part of the Level 1 analysis. Two models were estimated in which the function of time was linear and quadratic. For evening fatigue, the likelihood ratio tests indicated that a quadratic model fit the data significantly better than a linear model ($p < .001$). For morning fatigue, the linear model ($p = .02$) was a better fit than the quadratic model ($p = .39$).

Evening Fatigue—The estimates of the quadratic change model are presented in Table 4 (unconditional model). Because the model has no covariates (i.e., unconditional), the intercept represents the estimate of the severity of evening fatigue in FCs (i.e., 4.335 on a 0 to 10 scale) at the time of the patient's simulation visit. The estimated linear rate of change in evening fatigue for each additional week was 0.1256 ($p = .025$) and the estimated quadratic change per week was $-.004$ ($p = .001$). The weighted combination of the linear and quadratic terms defined the curve.

Figure 1 displays the trajectory for evening fatigue in FCs from the time of the patient's simulation visit to 4 months after the completion of RT. Evening fatigue in FCs increased over the course of the patients' RT and then declined after the completion of RT. It should be noted that the mean fatigue severity scores for the various groups depicted in all of the figures are estimated or predicted means based on the HLM analyses (i.e., these are not actual values but estimated values).

Morning Fatigue—The unconditional model is shown in Table 4 and the intercept represents the estimated severity of morning fatigue in FCs (i.e., 2.636) at the time of the simulation visit. The estimated linear rate of change for each additional week was $-.018$ ($p = .006$). Figure 1 displays the trajectory for morning fatigue in FCs from the time of the patient's simulation visit to 4 months after the completion of RT. Morning fatigue decreased slightly over time.

Although these Level 1 sample wide results indicate uniform changes over time, they do not imply that all FCs exhibited the same fatigue trajectory. The variance in individual change parameters estimated by the models (i.e., variance components, Table 4) suggested that substantial inter-individual differences existed in the trajectories of evening and morning fatigue (Figures 2A and 2B, respectively). Thus, further examination of the inter-individual differences in the individual change parameters was warranted.

Predictors of Inter-individual Differences in Fatigue in Family Caregivers

The second research question, addressing whether characteristics of the FC (i.e., personal, environmental, health/illness, symptoms) as well as of the patient (i.e., personal, disease, symptoms) influenced the trajectories of evening and morning fatigue in FCs, was tested in the Level 2 analyses. Exploratory analyses were completed with all of the potential predictor variables listed in Table 3. To improve estimation efficiency and construct models that were parsimonious, exploratory Level 2 analyses were done in which each potential predictor was assessed to see if it would result in a better fitting model if it alone was added as a Level 2 predictor. Predictors with a t -value of < 2.0 were dropped from subsequent model testing. All of the significant predictors from these exploratory analyses were entered into the models to predict each individual change parameter (i.e., intercepts and/or slopes). Only those predictors that maintained a significant contribution in conjunction with other variables were retained in the final models of evening and morning fatigue in FCs.

Evening Fatigue in FCs—Table 4 shows the final model for evening fatigue in FCs. The two variables that predicted inter-individual differences in the *intercept* for evening fatigue (i.e., baseline level of fatigue at the time of the simulation visit) were baseline level of sleep disturbance in FCs and baseline level of evening fatigue in patients. Baseline level of evening fatigue in FCs was entered in Level 2 as a predictor of the slope parameters to control for intra-individual differences in FCs' evening fatigue at baseline. Baseline level of evening fatigue in FCs was the one variable that predicted inter-individual differences in the *slope* parameters for evening fatigue.

In order to illustrate the effects of all of the different predictors on the trajectories of evening fatigue in FCs, Figure 3 displays the adjusted change curves of evening fatigue that were estimated based on differences in baseline levels of FCs' sleep disturbance (i.e., high or low sleep disturbance based on 1 standard deviation (SD) above and below the FCs' mean baseline GSDS score), baseline levels of evening fatigue in patients (i.e., high or low baseline evening fatigue based on 1 SD above or below the patients' mean evening LFS score), and baseline level of FCs' evening fatigue (i.e., high and low fatigue based on 1 SD above and below the FCs' mean baseline evening LFS score).

Morning Fatigue in FCs—Table 4 shows the final model for morning fatigue in FCs. The three variables that predicted inter-individual differences in the *intercept* for morning fatigue were baseline levels of trait anxiety in FCs, baseline levels of family support, and baseline levels of morning fatigue in patients. Baseline level of morning fatigue in FCs was entered in Level 2 as a predictor of the slope parameters to control for inter-individual

differences in morning fatigue in FCs at baseline. No predictors were found for change in morning fatigue over time (i.e. linear *slope*).

To illustrate the effects of all of the different predictors on the trajectories of morning fatigue in FCs, Figure 4 displays the adjusted change curves of morning fatigue according to differences in baseline levels of FCs' trait anxiety (i.e., high or low trait anxiety based on 1 *SD* above and below the FCs' mean baseline trait anxiety score), baseline levels of family support (i.e., high or low levels of family support based on 1 *SD* above and below the mean baseline CRA - lack of family support score), and baseline levels of morning fatigue in patients (i.e., high or low levels of morning fatigue based on 1 *SD* above or below the patients' mean baseline morning LFS score).

Discussion

Intra-Individual Changes in Evening and Morning Fatigue in Family Caregivers

To our knowledge, we are the first research team to examine intra-individual differences in the trajectories of evening and morning fatigue in FCs of patients who underwent RT for prostate cancer and to determine the predictors of inter-individual differences in these trajectories. While direct comparisons are not possible because previous researchers did not distinguish between evening and morning fatigue in FCs, our findings from the unconditional model of evening fatigue are consistent with findings from longitudinal studies of *patients* with prostate cancer (Choo et al., 2007; Hickok et al., 2005; Miaskowski et al., 2008; Monga, Kerrigan, Thornby, Monga, & Zimmermann, 2005) demonstrating increases in fatigue severity during RT followed by decreases in fatigue after the completion of RT. In addition, these findings are consistent with the only other descriptive longitudinal study of fatigue in FCs (Passik & Kirsh, 2005). However, given the paucity of longitudinal research on fatigue in FCs of oncology patients, additional research is warranted to determine if similar fatigue trajectories occur in other groups of FCs whose patients have different cancer diagnoses, are receiving different types of cancer treatments, or are in different stages of their disease process.

The finding that evening fatigue was higher than morning fatigue at baseline and across the 6 months of the study is consistent with previous cross-sectional studies (Lee et al., 1991; Lee et al., 1999), as well as the findings from two longitudinal studies of *patients* with cancer (Dimsdale et al., 2007; Miaskowski et al., 2008). This finding lends additional support to the need to evaluate for diurnal variations in fatigue severity because as suggested by others (Curran et al., 2004; Hacker & Ferrans, 2007; Schubert, Hong, Natarajan, Mills, & Dimsdale, 2007), this approach may provide broader insights into the etiologies of fatigue in both patients and their FCs.

While evening fatigue in FCs fit a quadratic model, morning fatigue fit a linear model. This finding conflicts with a previous report of fatigue trajectories in patients with prostate cancer that found that both evening and morning fatigue fit a quadratic model (Miaskowski et al., 2008). One potential explanation for these different trajectories is that different factors may influence the development of fatigue in patients and FCs. This hypothesis is supported by the finding that while some of the same predictors were associated with patients' and FCs' fatigue trajectories (e.g., baseline levels of evening and morning fatigue), others were unique to patients (e.g., age, baseline level of depression) and to FCs (e.g., lack of family support, evening and morning fatigue levels of patients). An alternative hypothesis is that some of the biologic mechanisms that underlie the development of fatigue are different for patients (e.g., cancer) and FCs (e.g., other chronic medical conditions). While these conclusions may seem obvious, they contribute a great deal to the limited knowledge about fatigue in FCs of oncology patients.

As illustrated in Figure 2, the use of HLM, rather than more traditional statistical methods to evaluate change over time revealed substantial inter-individual variability in the trajectories of evening and morning fatigue. This finding is consistent with clinical observations and provides insights that may be helpful in determining which FCs are at increased risk for evening and morning fatigue, and as such, warrants replication in FCs of patients with different chronic medical conditions.

Predictors of Inter-individual Differences in Evening Fatigue in Family Caregivers

For evening fatigue, the FCs' baseline level of sleep disturbance, as well as the patients' baseline level of evening fatigue predicted inter-individual differences in evening fatigue severity at the time of the simulation visit (i.e., intercept). When the other predictors were held constant, FCs' evening fatigue scores ranged from 2.69 to 6.57. Of note, for every one unit increase in patient's evening fatigue scores, FCs' level of fatigue increased by .35 units which is consistent with a previous report (Curt et al., 2000). However, our findings differ from those of Passik & Kirsh (2005), who found no relationship between patients' and FCs' ($n=25$) fatigue scores. These differences may be related to the larger sample size in our study. In addition, the patients' baseline level of morning fatigue predicted FCs' baseline level of morning fatigue. Taken together, these findings suggest that studies of symptoms in FCs need to include an evaluation of symptoms in the patients, particularly if the purpose of the study is to determine the predictors of symptom severity in FCs.

Consistent with findings from the *patient* cohort (Miaskowski et al., 2008), baseline levels of sleep disturbance in FCs predicted inter-individual differences in FC baseline evening fatigue. This finding is congruent with work by Cho et al. (2006), who reported a positive correlation between sleep disturbance and fatigue in a cross-sectional study of FCs of oncology patients. Finally, after controlling for FCs' baseline level of evening fatigue, baseline level of sleep disturbance predicted inter-individual variability in both the linear and quadratic components of the evening fatigue trajectories. An identical relationship was found in the patient cohort, which suggests that clinicians need to assess both oncology patients and their FCs for sleep disturbance at the initiation of RT.

When the final HLM model of evening fatigue was constructed, eight different fatigue trajectories were identified based on three predictors of inter-individual variability. As illustrated in Figure 3, two distinct groups of trajectories are evident that are influenced by baseline levels of fatigue in the FCs. Family caregivers with lower levels of evening fatigue at baseline exhibited trajectories that gradually increased during the course of the patients' RT and then decreased following the completion of RT. Family caregivers with higher levels of evening fatigue at baseline exhibited trajectories of evening fatigue that gradually increased over the course of the patients' RT. The predictor that influenced the overall severity of the fatigue trajectories was the FC's level of sleep disturbance at baseline. Family caregivers with higher levels of baseline sleep disturbance with either high or low levels of patient or FC evening fatigue at baseline had the higher evening fatigue scores over time. This finding suggests that assessing for FC sleep disturbances and interventions to improve FC sleep may be needed to reduce fatigue.

Predictors of Inter-Individual Differences in Morning Fatigue in FCs

As shown in Table 4, the predictors of morning fatigue at the time of the simulation visit (i.e., intercept) were: FCs' baseline level of trait anxiety, baseline level of family support, and patients' baseline level of morning fatigue. However, no predictors of the linear slope were identified in this analysis. Also noteworthy is the finding that the predictors of baseline levels of morning fatigue in FCs, differed completely from those that predicted baseline levels of morning fatigue in *patients* in this cohort (i.e., age, baseline level of sleep

disturbance, and baseline level of depression) (Miaskowski et al., 2008). One potential reason for these differences may be that all of the FCs were women, while the patients were all men. However, this finding warrants additional investigation.

As shown in Figure 4, all eight trajectories for morning fatigue decreased over time. FCs with the highest levels of morning fatigue reported higher levels of trait anxiety, lower levels of family support, and cared for patients with higher levels of morning fatigue at the time of the simulation visit. The morning fatigue scores reported by these FCs ($M = 4.63$) were above the cutpoint for clinically significant levels of morning fatigue (i.e., ≥ 3.2 on the LFS; Fletcher et al., 2008). In only one other study was a positive association between anxiety and fatigue found in FCs of oncology patients (Gaston-Johansson et al., 2004).

Limitations

Study limitations include the homogenous characteristics of the sample (i.e., all female, all FCs of patients with prostate cancer); the focus on a single treatment modality (i.e., RT); the relatively small sample size, and low Cronbach's alpha for the CRA subscales. Therefore, these findings may not generalize to other FC populations. Additional research is warranted to confirm these findings as well as to evaluate the fatigue trajectories of other groups of FCs of oncology patients.

Implications for Research

Findings from this study, as well as from the initial study of patients with prostate cancer (Miaskowski et al., 2008), suggest that a mixed models approach such as HLM is a useful statistical approach to analyze longitudinal data on symptoms. This approach not only provided the group level data of more traditional analyses, but also provided evidence of a large amount of inter-individual variability in the trajectories of evening and morning fatigue in these FCs.

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Figure 1.
Trajectories of evening and morning fatigue over the 25 weeks of the study

Figure 2A

Figure 2B

Figure 2. Spaghetti plots of the individual trajectories of evening (A) and morning (B) fatigue over the 25 weeks of the study

Figure 3.

Trajectories of evening fatigue by level of sleep disturbance at baseline (i.e., low sleep/high sleep), level of evening fatigue in patients at baseline (low PT fatigue/high PT fatigue), and level of FC evening fatigue at baseline (i.e., low FC fatigue/high FC fatigue)

Figure 4.

Trajectories of morning fatigue by level of FC trait anxiety at baseline (i.e., low FC anxiety/high FC anxiety), level of morning fatigue in patients at baseline (i.e., low PT fatigue/high PT fatigue), and level of FC morning fatigue at baseline (i.e., low FC fatigue/high FC fatigue)

Table 1

Demographic Characteristics and Comorbid Conditions of the Family Caregivers and Patients (n = 60)

Characteristic	Family caregivers	Patients
	Mean (Standard Deviation)	Mean (Standard Deviation)
Age (years)	64.2 (8.8)	68.1 (7.9)
Education (years)	15.2 (2.8)	16.6 (3.2)
KPS score	94.0 (10.5)	96.8 (5.5)
	%	%
Marital status		
Married/partnered	93.3	93.3
Other	6.7	6.7
Ethnicity		
Black	11.7	13.3
White	80.0	81.7
Other	8.3	5.0
Employed		
Yes	36.7	44.1
Comorbid Conditions*		
Back problems	48.3	59.3
Arthritis	41.7	36.2
Hypertension	35.0	32.8
Headaches	35.0	19.0
Hemorrhoids	28.3	31.0
Symptoms at Baseline	Mean (Standard Deviation)	Mean (Standard Deviation)
Evening fatigue (LFS)	4.3 (2.3)	3.5 (2.1)
Morning fatigue (LFS)	2.5 (2.1)	1.8 (1.8)
Sleep disturbance (GSDS)	39.9 (16.2)	34.7 (16.8)
Depression (CES-D)	8.4 (6.5)	5.9 (5.9)
State anxiety (STAI-S)	32.6 (10.6)	27.5 (7.5)
Trait anxiety (STAI-T)	35.3 (9.6)	30.9 (8.2)
Worst pain	1.4 (3.1)	1.2 (3.0)

* Family caregivers and patients could report more than one comorbid condition.

Abbreviations: CES-D = Center for Epidemiologic Studies – Depression Scale; GSDS = General Sleep Disturbance Scale; KPS = Karnofsky Performance Status; LFS = Lee Fatigue Scale; STAI-S = Spielberger State Anxiety Inventory; STAI-T = Spielberger Trait Anxiety Inventory

Table 2

Disease and Treatment Characteristics of the Patients (n = 60)

Characteristic	%
Gleason score	
5 or 6	40.0%
7	46.7%
≥ 8	5.0%
Clinical stage	
T1	46.7%
T2	40.0%
T3	10.0%
Prostatectomy prior to RT	11.7%
Hormonal therapy prior to RT	51.7%
RT treatment plan	
Whole pelvis + conformal boost after surgery	11.7%
Whole pelvis + conformal boost	70.0%
Whole pelvis + high dose RT	5.0%
Whole pelvis + seed implant	13.3%
	<u>Mean (standard deviation)</u>
Total dose of RT (cGys)	6851 (1024.2)
Time since diagnosis (months)	9.7 (15.1)

Note: Abbreviations: cGys = dose of RT in centigray units, RT = radiation therapy.

Table 3
Potential Predictors of Intercept (I), Linear Coefficient (LC) and Quadratic Coefficient (QC) for Evening and Morning Fatigue

Potential Family Caregiver Predictors		Evening Fatigue		Morning Fatigue	
Person		I	LC	I	LC
Age					
Relationship to patient					
Ethnicity					
Marital status					
Education					•
Employment status					
CRA Caregiver's esteem					
Environment					
CRA Impact on schedule					
CRA Lack of family support				•	
CRA Impact on finances					
Health and Illness					
KPS score					
Number of co-morbidities					
CRA Impact on Health					
Symptoms					
Baseline GSDS score	•		•		
Baseline CES-D score	•		•	•	
Presence of pain at baseline					
Baseline STAI-T score				•	
Baseline STAI-S score				•	
Potential Patient Predictors					
Person					
Age	•			•	
Ethnicity					
Education					

Potential Family Caregiver Predictors	Evening Fatigue			Morning Fatigue		
	I	LC	QC	I	LC	QC
Person						
Employment status						
Health and Illness						
KPS score						
Number of co-morbidities						
Symptoms						
Baseline GSDS score	▪	▪	▪	▪	▪	▪
Baseline CES-D score	▪	▪	▪	▪	▪	▪
Presence of pain at baseline						
Baseline STAI-T score				▪		
Baseline STAI-S score						
Baseline evening LFS score	▪			▪		
Baseline morning LFS score				▪		

Note * = From exploratory analysis had a t-value > 2.00

Abbreviations: CES-D = Center for Epidemiologic Studies – Depression; CRA = Caregiver Reaction Assessment; GSDS = General Sleep Disturbance Scale; KPS = Karnofsky Performance Status; LFS = Lee Fatigue Scale; STAI-S = Spielberger State Anxiety Inventory; STAI-T = Spielberger Trait Anxiety Inventory

Table 4

Hierarchical Linear Models of Evening and Morning Fatigue in Family Caregivers

Evening Fatigue	Coefficient (SE)	
Variable	Unconditional Model	Final Model
Fixed Effects		
Intercept	4.34 (.249)*	4.34 (.211)*
Time ^a (linear rate of change)	.13 (.025)*	.13 (.027)*
Time ² (quadratic rate of change)	-.004 (.001)*	-.004 (.001)*
Time invariant covariates ^b		
Intercept		
Baseline sleep disturbance in FC		.06 (.012)*
Baseline evening fatigue in patients		.35 (.092)*
Linear		
Baseline evening fatigue in FC × time		-.04 (.012)**
Quadratic		
Baseline evening fatigue in FC × time ²		.002 (.0005)**
Variance components		
In intercept	3.32*	2.28*
In linear rate	.02*	.03*
In quadratic fit	.00003*	.00004*
Goodness-of-fit deviance(parameters estimated)	2886.01 (10)	2854.03 (14)
Model comparison (X ² [df])		31.98 (4)*
Morning Fatigue	Coefficient (SE)	
Variable	Unconditional Model	Final Model
Fixed Effects		
Intercept	2.64 (.242)*	2.64 (.190)*
Time ^a (linear rate of change)	-.02 (.006)***	-.02 (.006)***
Time invariant covariates ^b		
Intercept		
Baseline trait anxiety in FCs		.09 (.020)*
Baseline lack of family support		.57 (.266)++
Baseline morning fatigue in patients		.41 (.104)*
Linear		
Baseline morning fatigue in FC × time		-.002 (.003)

Evening Fatigue	Coefficient (SE)	
Variable	Unconditional Model	Final Model
Variance components		
In intercept	3.29 [*]	1.96 [*]
In linear rate	0.001 ⁺	0.001 ⁺
Goodness-of-fit deviance(parameters estimated)	2838.73 (6)	2809.36 (10)
Model comparison (X^2 [df])		29.38 (4) [*]

^{*} p < .001,

^{**} p = .001,

^{***} p = .005,

⁺ p = .02

⁺⁺ p = .04,

^aTime was coded 0 at the time of the simulation visit

^bTime invariant covariates based on literature review of fatigue in FCs and patients

Abbreviations: FC = family caregiver