Title
Morning Fatigue Severity Profiles in Oncology Outpatients Receiving Chemotherapy.

Journal
Cancer nursing, 42(5)

ISSN
0162-220X

Authors
Wright, Fay
Dunn, Laura B
Paul, Steven M
et al.

Publication Date
2019-09-01

DOI
10.1097/ncc.0000000000000626

Peer reviewed

HHS Public Access

Author manuscript

Cancer Nurs. Author manuscript; available in PMC 2020 September 01.

Published in final edited form as:

Cancer Nurs. 2019 ; 42(5): 355–364. doi:10.1097/NCC.0000000000000626.

Morning Fatigue Severity Profiles in Oncology Outpatients Receiving Chemotherapy

Dr Fay Wright, RN, PhD,
School of Nursing, Yale University, New Haven, CT

Dr Laura B. Dunn, MD,
School of Medicine, Stanford University, Palo Alto, CA

Dr Steven M. Paul, PhD,
School of Nursing, University of California, San Francisco, CA

Dr Yvette P. Conley, PhD,
School of Nursing, University of Pittsburgh, Pittsburgh, PA

Dr Jon D. Levine, MD, PhD,
School of Medicine, University of California, San Francisco, CA

Dr Marilyn J. Hammer, RN, PhD,
Mount Sinai Medical Center, New York, NY

Dr Bruce A. Cooper, PhD,
School of Nursing, University of California, San Francisco, CA

Dr Christine Miaskowski, RN, PhD,
School of Nursing, University of California, San Francisco, CA

Dr Kord M. Kober, PhD
School of Nursing, University of California, San Francisco, CA

Abstract

Background—Morning fatigue is a distinct symptom experienced during chemotherapy (CTX) that demonstrates significant inter-individual variability.

Objective—To identify subgroups with distinct morning fatigue profiles and evaluate how these subgroups differed by demographic, clinical, and symptom characteristics.

Methods—Outpatients (N=1332) with breast, gastrointestinal, gynecological or lung cancer completed questionnaires six times over two cycles of chemotherapy. Morning fatigue was assessed with the Lee Fatigue Scale (LFS). Latent profile analysis was used to identify distinct morning fatigue profiles.

Correspondence: Kord Kober, PhD, Department of Physiological Nursing, University of California, 2 Koret Way – N631Y, San Francisco, CA 94143-0610 (Kord.Kober@ucsf.edu).

Conflicts of Interest: The authors have no conflicts of interest to disclose.

Results—Four morning fatigue profiles (i.e., Very Low, Low, High, and Very High) were identified. In the High and Very High classes, all six morning fatigue scores were above the clinical cutoff score. Compared to Very Low and Low classes, patients in the Very High class were younger, not married/partnered, lived alone, had higher incomes, had higher comorbidity, had higher BMI, and did not exercise regularly. Across the four classes, functional status and attentional function scores decreased and anxiety, depression, sleep disturbance, morning fatigue, and evening fatigue scores increased across the two cycles.

Conclusions—Results provide insights into modifiable risk factors for morning fatigue. These risk factors can be used to develop more targeted interventions.

Implications for Practice—Patients in the High and Very High morning fatigue classes experienced high symptom and high comorbidity burdens and significant decrements in functional status. Using this information, clinicians can identify patients who are at increased risk for higher levels of morning fatigue and prescribe interventions to improve this devastating symptom.

Introduction

Fatigue is a highly prevalent symptom for patients during chemotherapy (CTX).[1] While work by our team demonstrated that morning fatigue is distinct from evening fatigue,[2–6] research on morning fatigue is limited. Newer analytic techniques, like latent profile analysis (LPA), can facilitate the identification of patients at higher risk for more severe symptoms.

Techniques like LPA, group individuals into classes with similar outwardly unobservable characteristics.[7] Only three studies were identified that used this approach to identify groups of patients with distinct fatigue profiles.[3,8,9] In the two studies, that evaluated average fatigue scores in patients with breast cancer before surgery and after CTX or radiation therapy,[8,9] two latent classes (i.e., Higher and Lower Fatigue) were identified. It is difficult to compare findings across these studies because the measures of fatigue and timing of assessments differed. Neither study examined diurnal variations in fatigue severity.

In the third study,[3] we identified three distinct morning fatigue profiles (i.e., Low, High, Very High). Compared to the Low class, patients in the Very High class were more likely to be younger, female, with a higher BMI, less likely to be married/partnered or to exercise regularly. In addition, they had a lower annual income, a lower functional status, and a worse comorbidity profile. To develop targeted interventions for patients who are at risk for higher levels of morning fatigue, additional studies are needed to refine these profiles. Therefore, the purposes of this study, using a larger sample (n=1332) were to evaluate for subgroups of patients with distinct morning fatigue profiles; evaluate how these subgroups differed on demographic, clinical, and symptom characteristics; and confirm our previous morning fatigue LPA findings.[3]

Methods

Patients and Settings

Methods for this study were published previously.[3,4,10] In brief, patients were diagnosed with breast, gastrointestinal (GI), gynecological (GYN), or lung cancer; had received CTX

within the preceding month; were scheduled for two additional CTX cycles; were adults (≥18 years old); could read, write, and understand English; and gave written informed consent. Patients were recruited from seven outpatient settings.

Instruments

Information was obtained on various demographic characteristics. The Alcohol Use Disorders Identification Test (AUDIT) was used to assess alcohol consumption. Scores of ≥8 are defined as hazardous use and scores of ≥16 out of 40 are defined as use of alcohol that is likely to be harmful to health. The AUDIT has well established validity and reliability in the general population.[11] In our study, its Cronbach's alpha was 0.63.

Functional status was evaluated using the Karnofsky Performance Status (KPS) scale.[12] For the Self-Administered Comorbidity Questionnaire (SCQ), patients indicated if they had 13 common medical conditions; if they received treatment for any of them; and if each condition limited their activities. The total SCQ score ranges from 0 to 39. The SCQ has well established validity and reliability in inpatient populations.[13]

Fatigue was evaluated using the Lee Fatigue Scale (LFS). Each of the 18 items was 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 5 energy items, respectively. Higher scores indicate greater fatigue severity and higher levels of energy. Using separate LFS, patients rated each item based on how they felt within 30 minutes of awakening (i.e., morning fatigue, morning energy) and prior to going to bed (i.e., evening fatigue, evening energy). The LFS has established cut-off scores for clinically meaningful levels of fatigue (i.e., ≥3.2 for morning fatigue, ≥5.6 for evening fatigue) and energy (i.e., ≤6.2 for morning energy, ≤3.5 for evening energy). The LFS has well established validity and reliability in the general population.[14] In our study, the Cronbach's alphas were 0.96 for morning and 0.93 for evening fatigue and 0.95 for morning and 0.93 for evening energy.

Trait and state anxiety were measured using Spielberger State-Trait Anxiety Inventories (STAI-S and STAI-T). Total scores range from 20 to 80. Cutoff scores of ≥31.8 and ≥32.2 indicate high levels of trait and state anxiety, respectively. The STAI-T and STAI-S have well established validity and reliability in the general population.[15] In our study, the Cronbach's alphas for the STAI-T and STAI-S were 0.92 and 0.96, respectively.

Depressive symptoms were evaluated using the Center for Epidemiological Studies-Depression scale (CES-D). The total CES-D score ranges from 0 to 60. Scores of ≥16 indicate the need for individuals to seek clinical evaluation for major depression. The CES-D has well established validity and reliability in the general population.[16] In our study, its Cronbach's alpha was 0.89.

Sleep disturbance was evaluated using the General Sleep Disturbance Scale (GSDS) which assesses the quality of sleep in the past week. Each item was rated on a 0 (never) to 7 (everyday) NRS. A total GSDS score of ≥43 indicates a significant level of sleep disturbance.[17] The GSDS has well established validity and reliability in the general population.[17] In our study, its Cronbach's alpha was 0.83.

Changes in cognitive function were evaluated using the Attentional Function Index (AFI). Higher total mean AFI scores indicate greater capacity to direct attention. Total scores are grouped into three categories of attentional function (i.e., <5.0 low function, 5.0 to 7.5 moderate function, >7.5 high function). The AFI has well established reliability and validity in oncology patients.[18] In our study, its Cronbach's alpha was 0.93.

The Brief Pain Inventory was used to assess the occurrence of pain.[19] Patients who indicated that they had pain were asked if their pain was or was not related to their cancer treatment.

Study Procedures

The Committees on Human Research at the University of California, San Francisco and at each of the study sites approved the study. Patients were approached in the infusion unit by a research staff member to discuss participation in the study. Written informed consent was obtained from all patients. Depending on their CTX cycle length, patients completed the various questionnaires in their homes, a total of six times over two cycles of CTX (i.e., prior to CTX administration, approximately 1 week after CTX administration, approximately 2 weeks after CTX administration).

Data Analysis

SPSS version 23 (Armonk, NY) was used to calculate descriptive statistics for the sample characteristics. LPA was used to identify subgroups of patients with distinct morning fatigue profiles. Estimation was carried out with full information maximum likelihood with standard errors and a Chi-square test that are robust to non-normality and non-independence of observations. The Akaike Information Criteria, Bayesian Information Criterion, and entropy values were used to determine the best fitting model. Vuong-Lo-Mendell-Rubin likelihood ratio test (VLMR) was used to compare the models. With the VLMR, a significant p-value suggests that one estimated model fits the data better than another model with one fewer groups.[20] The LPA was done using Mplus Version 7.2 (Muthen & Muthen, Los Angeles, CA) with 1,000 to 2,400 random starts.

Differences in demographic and clinical characteristics among the latent classes were evaluated using parametric and nonparametric tests with Bonferroni corrected post hoc contrasts. A p-value of <.05 was considered statistically significant.

Results

Latent class analysis

Based on the fit indices, a four-class solution was selected (Table 1). Morning fatigue classes were labeled: Very Low, Low, High, and Very High based on the morning LFS cut-off score of ≥3.2. The trajectories of morning fatigue differed among the latent classes (Figure). For the Very Low (19.6%) and Very High (10.6%) classes, morning fatigue scores remained relatively stable across the six assessments. For the Low (30.2%) and High (39.6%) classes, morning fatigue scores exhibited a distinct increase at the second and fifth assessments.

Demographic and clinical characteristics

For the majority of the demographic and clinical characteristics, no differences were found among the latent classes (Table 2). Compared to the Very Low and Low classes, patients in the Very High class were more likely to: be younger, not married/partnered, live alone, have lower incomes, have a higher number of comorbidities, a higher SCQ score, a higher BMI, and were less likely to exercise regularly. Compared to the Very Low class, patients in the Very High class were more likely to be female. Compared to the Low class, a higher percentage of patients in the Very High class were more likely to be unemployed. Compared to the Very Low class, patients in the High class were more likely to be diagnosed with breast cancer. Across the four classes, as morning fatigue severity increased, KPS scores decreased (i.e., Very Low>Low>High>Very High for KPS scores) and the occurrence of depression increased (i.e., Very Low<Low<High< Very High). Patients in the Very High class were more likely to report anemia than patients in the Low and Very Low classes.

Symptom characteristics at enrollment

For the trait anxiety, state anxiety, depression, sleep disturbance, morning fatigue, and evening fatigue scores, significant differences were found among the latent classes (i.e., Very Low<Low<High<Very High, Table 3). Attentional function scores were significantly different among the four classes (i.e., Very Low>Low>High>Very High). For morning energy, patients in the Very Low class had higher scores than the other three classes and the Low class had higher scores than the High and Very High classes. For evening energy, compared to patients in the other three classes, patients in the Very High class had lower scores. Compared to the Very Low and Low classes, a higher percentage of patients in the High and Very High classes, reported both cancer and non-cancer pain.

Discussion

This study extends our prior work on the identification of distinct morning fatigue profiles in oncology patients. While in our previous study,[3] three morning fatigue profiles were identified, in this study, with the addition of 750 patients, four profiles were found. In this study, a Very Low class was identified using the clinically meaningful cutoff score for morning fatigue. Compared to the Low class in the previous study who had a mean enrollment LFS score of 1.3,[3] the LFS score for the Very Low class in this study was 0.9. This clinically meaningful difference (d=.77) in LFS scores,[21] supported the identification of a fourth latent class and the refinement of the morning fatigue phenotype. In the High and Very High classes, which included 50.2% of our sample, morning fatigue scores were above the LFS clinically meaningful cutoff score (i.e., ≥3.2) across all six assessments. The high prevalence of morning fatigue suggests that clinicians need to assess for diurnal variations in fatigue severity.

Modifiable Risk Factors

One of our goals was to identify modifiable characteristics associated with more severe morning fatigue. Based on our previous[3] and current LPA and HLM analyses,[4] the phenotypic characteristics associated with higher morning fatigue scores and membership in the Very High morning fatigue classes are summarized in Table 4. The remainder of the

discussion describes these phenotypic characteristics within the context of the literature on morning fatigue.

Consistent with our prior studies,[3,4] younger age and being female were associated with higher levels of morning fatigue. Across other studies, younger patients reported higher average fatigue severity scores.[22] "response shifts",[23] age-related changes in inflammatory responses,[24] and different treatment regimens[25] may explain this association. It is difficult to determine if gender is an independent predictor of higher levels of morning fatigue because this association may be confounded by the high percentage of patients with female cancers enrolled in our study.

In contrast to our HLM findings,[4] in this LPA, living alone, marital/partnership status, income level, and employment status were associated with a worse morning fatigue profile. Consistent with previous findings,[26] patients in the Very High class were less likely to be employed than patients in the Low class and more likely to have higher incomes than patients in the other three classes. Higher incomes may mitigate the financial burden of cancer treatment and its negative impact on patients' symptom burden.[27] Consistent with previous findings,[26] patients in the Very High morning fatigue class were more likely not to be married/partnered and to be living alone. While these demographic characteristics are not easily modified, knowledge of these risk factors can be used to guide appropriate referrals.

Consistent with our previous findings,[3,4] lack of regular exercise was associated with membership in the Very High morning fatigue class. While exercise is the only effective intervention to decrease fatigue,[28] no studies have evaluated the efficacy of exercise for morning fatigue. An emerging area of research is an evaluation of the association between an individual's chronobiology and his/her physical activity preferences.[29] Of note, when CTX was administered based on chronotype (classified as a "morning" or "evening" person), treatment efficacy increased and symptoms decreased.[30] Future studies should evaluate for associations between patients' chronotype, preferences for exercise, and fatigue severity.

For both our HLM[4] and the current LPA, a higher BMI was associated with membership in the Very High morning fatigue class. Patients in the Very High class had an average BMI of 27.6 that is in the "overweight" range. Higher BMIs are associated with inflammation and may contribute to the inflammatory processes associated with morning fatigue.[24] As a modifiable risk factor, clinicians need to recommend weight loss and exercise programs to oncology patients to decrease fatigue and improve overall health status.

Consistent with our previous studies,[3,4] as well as other reports that evaluated average fatigue,[31,32] lower functional status was associated with higher levels of morning fatigue. Compared to the Very Low class, the differences in KPS scores for the other three classes were not only statistically significant, but clinically meaningful (i.e., d=0.3 [vs. Low], d=0.8 [vs. High], d=1.0 [vs. Very High]). Fatigue and physical function may be related through shared risk factors and/or common underlying mechanisms. Additional research is needed to elucidate these relationships.

Consistent with our prior LPA,[3] compared to the Very Low and Low classes, patients in the Very High class had a higher comorbidity burden. While associations were found between a higher comorbidity burden and increased fatigue,[33] whether or not each chronic condition contributes incrementally or synergistically to increases in fatigue severity, warrants investigation in future studies.

In contrast to our previous work in oncology patients receiving CTX,[3,4,10] specific comorbidities, hemoglobin, and hematocrit levels were associated with membership in the higher morning fatigue classes. Compared to the Very Low and Low classes, patients in the Very High class were more likely to self-report a diagnosis of anemia or blood disease. While the hemoglobin and hematocrit levels were similar among the three highest fatigue classes, significantly lower values were found between the Low and High classes compared to the Very Low class. The failure to identify a significant difference for the Very High class may be related to the relatively small sample size for this class. In patients undergoing CTX, anemia is defined as a hemoglobin level of <12 g/dL in both men and women.[34] While across the four classes, the average hemoglobin levels were <12 g/dL, the differences among the classes are not clinically meaningfully. Because findings regarding the association between anemia and fatigue severity are inconsistent,[35] future studies of the molecular mechanisms of fatigue may provide insights into these associations.

Patients with breast cancer were more likely to be in the Low and High classes than in the Very Low class. In contrast, compared to the other three classes, patients with GI cancer were more likely to be in the Very Low class. However, the number and types of prior cancer treatments and CTX cycle length were not associated with latent class membership. The associations among cancer diagnoses, treatment regimens, and fatigue severity warrant additional investigation.

This study is the first to demonstrate that for every symptom except energy and pain, statistically significant differences were found among the four latent classes in the most common symptoms experienced by oncology patients. Of note, for the High and Very High fatigue classes, except for depression, all of the symptom severity scores were above the clinically meaningful cutoff scores. For depression, patients in the High class had CES-D scores that indicate subsyndromal depression[16] and patients in the Very High class had scores that warrant evaluation for clinically significant depression.

While morning fatigue is considered a diagnostic criterion for depression, limited evidence exists to support a causal association or interdependence between these two symptoms. In one study,[36] higher levels of average fatigue were associated with increased evening cortisol levels and increased overall cortisol secretion but not with morning cortisol levels, independent of depression. Evaluation of distinct underlying mechanisms may provide insights into the co-occurrence of these two symptoms.

Consistent with our HLM analysis,[4] and our other studies of fatigue,[37,38] higher levels of anxiety and sleep disturbance were associated with higher levels of morning fatigue. The co-occurrence of these symptoms during CTX is well documented.[39] One possible explanation for the co-occurrence of these symptoms is that they are associated with alterations in

circadian rhythms.[40] Based on this evidence, clinicians can recommend individualized sleep promotion plans to regulate circadian rhythms and improve sleep disturbance.[41]

An assessment of attentional function evaluates patients' executive function, not physical fatigue.[18] In our patients, higher levels of morning fatigue were associated with lower levels of attentional function. Compared to the Very Low class, the differences in AFI scores of patients in the other three classes were not only statistically significant but clinically meaningful (i.e., d=0.6 [vs. Low], d =1.0 [vs. High], d=2.0 [vs. Very High]. This finding is consistent with previous studies that found that increases in physical fatigue were associated with decrements in cognitive function.[42,43] Inflammatory processes triggered by CTX[44] and/or dysregulation in cortisol rhythm or the hypothalamic–pituitary–adrenal (HPA) axis[36] are hypothesized mechanisms for these two co-occurring symptoms. However, research is needed to understand the bidirectional associations between decrements in attentional function and morning fatigue.

In terms of energy, only the High and Very High classes had clinically meaningful decrements in evening energy levels, with the Very Low and Low classes' evening energy levels at or below the clinical cutoff score. In contrast, morning energy levels were well below the cutoff score for all four latent classes. Often considered the opposite of fatigue, energy is defined as a person's potential to perform physical and mental activity.[45] In contrast, fatigue is a distressing and persistent sense of physical tiredness not related to physical activity.[1] Direct comparisons of our findings are not possible because no studies have evaluated morning and evening energy levels and morning fatigue in oncology patients during CTX. However, we found that decrements in morning and evening energy were associated with worse functional status and higher levels of sleep disturbance[46,47] and had distinct molecular mechanisms.[48] Future studies need to evaluate for associations among these three common co-occurring symptoms and their common and distinct molecular mechanisms.

While not found in our HLM analysis,[4] in this LPA, having cancer pain or non-cancer pain was associated with membership in the High and Very High morning fatigue classes. No studies have examined the association between pain and morning fatigue in oncology patients. While the exact causes of the pain in our patients are not known, pain, fatigue, and sleep disturbance are common co-occurring symptoms during CTX.[49, 50] Pain disrupts patients' sleep, decreases their ability to engage in physical activity, and increases fatigue. Pharmacologic treatments for pain may increase the severity of fatigue and sleep disturbance.

Limitations and Conclusions

Several limitations warrant consideration. Because patients were recruited at various time points during their CTX, risk profiles for morning fatigue from the initiation of CTX through its completion were not evaluated. While patients did not report the exact time that they completed the morning fatigue questionnaire, their ratings of morning fatigue were lower than evening fatigue. This finding supports the ecologic validity of the diurnal measurements. The findings related to exercise and pain need to be interpreted with caution given the limited amount of information collected on these two characteristics. However, this

large representative sample of oncology patients with diverse diagnoses, assessments of morning fatigue over two cycles of CTX, and the statistical approaches used to identify the latent classes are major strengths of this study.

Implications for Practice

This study increases our understanding of modifiable risk factors associated with distinct morning fatigue profiles. Patients in the High and Very High morning fatigue classes experienced high symptom and high comorbidity burdens and significant decrements in functional status. Using this information, clinicians can identify patients who are at increased risk for higher levels of morning fatigue and prescribe interventions to improve this devastating symptom. Additional research is warranted to evaluate for differences among these morning fatigue profiles based on a variety of psychosocial characteristics (e.g., resilience, coping) and genomic markers.

Acknowledgments

This study was funded by the National Cancer Institute (NCI; CA134900). Dr. Miaskowski is supported by a grant from the American Cancer Society and NCI (CA168960). Dr. Wright was funded by the National Institute of Nursing Research (T32NR008346).

References

1. Berger AM, Mooney K, Alvarez-Perez A, et al. Cancer-Related Fatigue, Version 2.2015. J Natl Compr Canc Netw. 2015; 13(8):1012–1039. [PubMed: 26285247]
2. Wright F, Hammer M, Paul SM, et al. Inflammatory pathway genes associated with inter-individual variability in the trajectories of morning and evening fatigue in patients receiving chemotherapy. Cytokine. 2017; 91:187–210. [PubMed: 28110208]
3. Kober KM, Cooper BA, Paul SM, et al. Subgroups of chemotherapy patients with distinct morning and evening fatigue trajectories. Support Care Cancer. 2016; 24(4):1473–1485. [PubMed: 26361758]
4. Wright F, D'Eramo Melkus G, Hammer M, et al. Predictors and Trajectories of Morning Fatigue Are Distinct From Evening Fatigue. J Pain Symptom Manage. 2015; 50(2):176–189. [PubMed: 25828559]
5. Dhruva A, Aouizerat BE, Cooper B, et al. Differences in morning and evening fatigue in oncology patients and their family caregivers. Eur J Oncol Nurs. 2013; 17(6):841–848. [PubMed: 24012189]
6. Dhruva A, Aouizerat BE, Cooper B, et al. Cytokine gene associations with self-report ratings of morning and evening fatigue in oncology patients and their family caregivers. Biol Res Nurs. 2015; 17(2):175–184. [PubMed: 24872120]
7. Jung T, Wickrama KAS. An introduction to latent class growth analysis and growth mixture modeling. Social and Personality Psychology Compass. 2008; 2(1):302–317.
8. Bodtcher H, Bidstrup PE, Andersen I, et al. Fatigue trajectories during the first 8 months after breast cancer diagnosis. Qual Life Res. 2015; 24(11):2671–2679. [PubMed: 25972303]
9. Kober KM, Smoot B, Paul SM, Cooper BA, Levine JD, Miaskowski C. Polymorphisms in cytokine genes are associated with higher levels of fatigue and lower levels of energy in women after breast cancer surgery. J Pain Symptom Manage. 2016; 52(5):695–708. [PubMed: 27664835]
10. Wright F, D'Eramo Melkus G, Hammer M, et al. Trajectories of evening fatigue in oncology outpatients receiving chemotherapy. J Pain Symptom Manage. 2015; 50(2):163–175. [PubMed: 25828560]
11. Berner MM, Kriston L, Bentele M, Harter M. The alcohol use disorders identification test for detecting at-risk drinking: a systematic review and meta-analysis. J Stud Alcohol Drugs. 2007; 68(3):461–473. [PubMed: 17446987]

12. Ando M, Ando Y, Hasegawa Y, et al. Prognostic value of performance status assessed by patients themselves, nurses, and oncologists in advanced non-small cell lung cancer. Br J Cancer. 2001; 85(11):1634–1639. [PubMed: 11742480]
13. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. Arthritis Rheum. 2003; 49(2):156–163. [PubMed: 12687505]
14. Lee KA, Hicks G, Nino-Murcia G. Validity and reliability of a scale to assess fatigue. Psychiatry Res. 1991; 36(3):291–298. [PubMed: 2062970]
15. Spielberger, CG, Gorsuch, RL, Suchene, R, Vagg, PR, Jacobs, GA. Manual for the State-Anxiety (Form Y): Self Evaluation Questionnaire. Palo Alto, CA: Consulting Psychologists Press; 1983.
16. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. Applied Psychological Measurement. 1977; 1(3):385–401.
17. Lee KA. Self-reported sleep disturbances in employed women. Sleep. 1992; 15(6):493–498. [PubMed: 1475563]
18. Cimprich B, Visovatti M, Ronis DL. The Attentional Function Index–a self-report cognitive measure. Psychooncology. 2011; 20(2):194–202. [PubMed: 20213858]
19. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. Pain. 1983; 17(2):197–210. [PubMed: 6646795]
20. Nylund KL, Asparoutiov T, Muthen BO. Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. Struct Equ Modeling. 2007; 14(4): 535–569.
21. Osoba D. Interpreting the meaningfulness of changes in health-related quality of life scores: lessons from studies in adults. Int J Cancer Suppl. 1999; 12:132–137. [PubMed: 10679884]
22. Soltow D, Given BA, Given CW. Relationship between age and symptoms of pain and fatigue in adults undergoing treatment for cancer. Cancer Nurs. 2010; 33(4):296–303. [PubMed: 20467311]
23. Schwartz CE, Sprangers MA. Methodological approaches for assessing response shift in longitudinal health-related quality-of-life research. Soc Sci Med. 1999; 48(11):1531–1548. [PubMed: 10400255]
24. Bower JE. Cancer-related fatigue–mechanisms, risk factors, and treatments. Nat Rev Clin Oncol. 2014; 11(10):597–609. [PubMed: 25113839]
25. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol. 2014; 32(24):2595–2603. [PubMed: 25071125]
26. Donovan KA, Small BJ, Andrykowski MA, Munster P, Jacobsen PB. Utility of a cognitive-behavioral model to predict fatigue following breast cancer treatment. Health Psychol. 2007; 26(4):464–472. [PubMed: 17605566]
27. Shankaran V, Jolly S, Blough D, Ramsey SD. Risk factors for financial hardship in patients receiving adjuvant chemotherapy for colon cancer: a population-based exploratory analysis. J Clin Oncol. 2012; 30(14):1608–1614. [PubMed: 22412136]
28. Furmaniak AC, Menig M, Markes MH. Exercise for women receiving adjuvant therapy for breast cancer. Cochrane Database Syst Rev. 2016; (9):CD005001. [PubMed: 27650122]
29. Wennman H, Kronholm E, Partonen T, Peltonen M, Vasankari T, Borodulin K. Evening typology and morning tiredness associates with low leisure time physical activity and high sitting. Chronobiol Int. 2015; 32(8):1090–1100. [PubMed: 26317556]
30. Innominato PF, Roche VP, Palesh OG, Ulusakarya A, Spiegel D, Levi FA. The circadian timing system in clinical oncology. Ann Med. 2014; 46(4):191–207. [PubMed: 24915535]
31. Fisch MJ, Zhao F, O'Mara AM, Wang XS, Cella D, Cleeland CS. Predictors of significant worsening of patient-reported fatigue over a 1-month timeframe in ambulatory patients with common solid tumors. Cancer. 2014; 120(3):442–450. [PubMed: 24151111]
32. Wang XS, Zhao F, Fisch MJ, et al. Prevalence and characteristics of moderate to severe fatigue: a multicenter study in cancer patients and survivors. Cancer. 2014; 120(3):425–432. [PubMed: 24436136]

33. Wright F, Hammer MJ, D'Eramo Melkus G. Associations between multiple chronic conditions and cancer-related fatigue: an integrative review. Oncol Nurs Forum. 2014; 41(4):399–410. [PubMed: 24849813]
34. Andres E, Serraj K, Federici L, Vogel T, Kaltenbach G. Anemia in elderly patients: new insight into an old disorder. Geriatr Gerontol Int. 2013; 13(3):519–527. [PubMed: 23253055]
35. Shafqat A, Einhorn LH, Hanna N, et al. Screening studies for fatigue and laboratory correlates in cancer patients undergoing treatment. Ann Oncol. 2005; 16(9):1545–1550. [PubMed: 15919683]
36. Schmidt ME, Semik J, Habermann N, Wiskemann J, Ulrich CM, Steindorf K. Cancer-related fatigue shows a stable association with diurnal cortisol dysregulation in breast cancer patients. Brain Behav Immun. 2016; 52:98–105. [PubMed: 26456694]
37. Dhruva A, Dodd M, Paul SM, et al. Trajectories of fatigue in patients with breast cancer before, during, and after radiation therapy. Cancer Nurs. 2010; 33(3):201–212. [PubMed: 20357659]
38. Miaskowski C, Paul SM, Cooper BA, et al. Predictors of the trajectories of self-reported sleep disturbance in men with prostate cancer during and following radiation therapy. Sleep. 2011; 34(2):171–179. [PubMed: 21286498]
39. Zhu L, Ranchor AV, van der Lee M, et al. Co-morbidity of depression, anxiety and fatigue in cancer patients receiving psychological care. Psychooncology. 2017; 26(4):444–451. [PubMed: 27193933]
40. Ancoli-Israel S, Liu L, Rissling M, et al. Sleep, fatigue, depression, and circadian activity rhythms in women with breast cancer before and after treatment: a 1-year longitudinal study. Support Care Cancer. 2014; 22(9):2535–2545. [PubMed: 24733634]
41. Berger AM, Kuhn BR, Farr LA, et al. Behavioral therapy intervention trial to improve sleep quality and cancer-related fatigue. Psychooncology. 2009; 18(6):634–646. [PubMed: 19090531]
42. Visovatti MA, Reuter-Lorenz PA, Chang AE, Northouse L, Cimprich B. Assessment of Cognitive Impairment and Complaints in Individuals With Colorectal Cancer. Oncol Nurs Forum. 2016; 43(2):169–178. [PubMed: 26906128]
43. Henneghan A. Modifiable factors and cognitive dysfunction in breast cancer survivors: a mixed-method systematic review. Support Care Cancer. 2016; 24(1):481–497. [PubMed: 26416490]
44. Bower JE, Ganz PA. Symptoms: Fatigue and Cognitive Dysfunction. Adv Exp Med Biol. 2015; 862:53–75. [PubMed: 26059929]
45. Lerdal A. A theoretical extension of the concept of energy through an empirical study. Scand J Caring Sci. 2002; 16(2):197–206. [PubMed: 12000674]
46. Aouizerat BE, Dhruva A, Paul SM, Cooper BA, Kober KM, Miaskowski C. Phenotypic and molecular evidence suggests that decrements in morning and evening energy are distinct but related symptoms. J Pain Symptom Manage. 2015; 50(5):599–614. [PubMed: 26031709]
47. Abid H, Kober KM, Smoot B, et al. Common and distinct characteristics associated with trajectories of morning and evening energy in oncology patients receiving chemotherapy. J Pain Symptom Manage. 2017; 53(5):887–900 e882. [PubMed: 28063861]
48. Eshragh J, Dhruva A, Paul SM, et al. Associations between neurotransmitter genes and fatigue and energy levels in women after breast cancer surgery. J Pain Symptom Manage. 2017; 53(1):67–84 e67. [PubMed: 27720787]
49. Cleeland CS, Zhao F, Chang VT, et al. The symptom burden of cancer: Evidence for a core set of cancer-related and treatment-related symptoms from the Eastern Cooperative Oncology Group Symptom Outcomes and Practice Patterns study. Cancer. 2013; 119(24):4333–4340. [PubMed: 24114037]
50. Kim HJ, Malone PS, Barsevick AM. Subgroups of cancer patients with unique pain and fatigue experiences during chemotherapy. J Pain Symptom Manage. 2014; 48(4):558–568. [PubMed: 24766741]

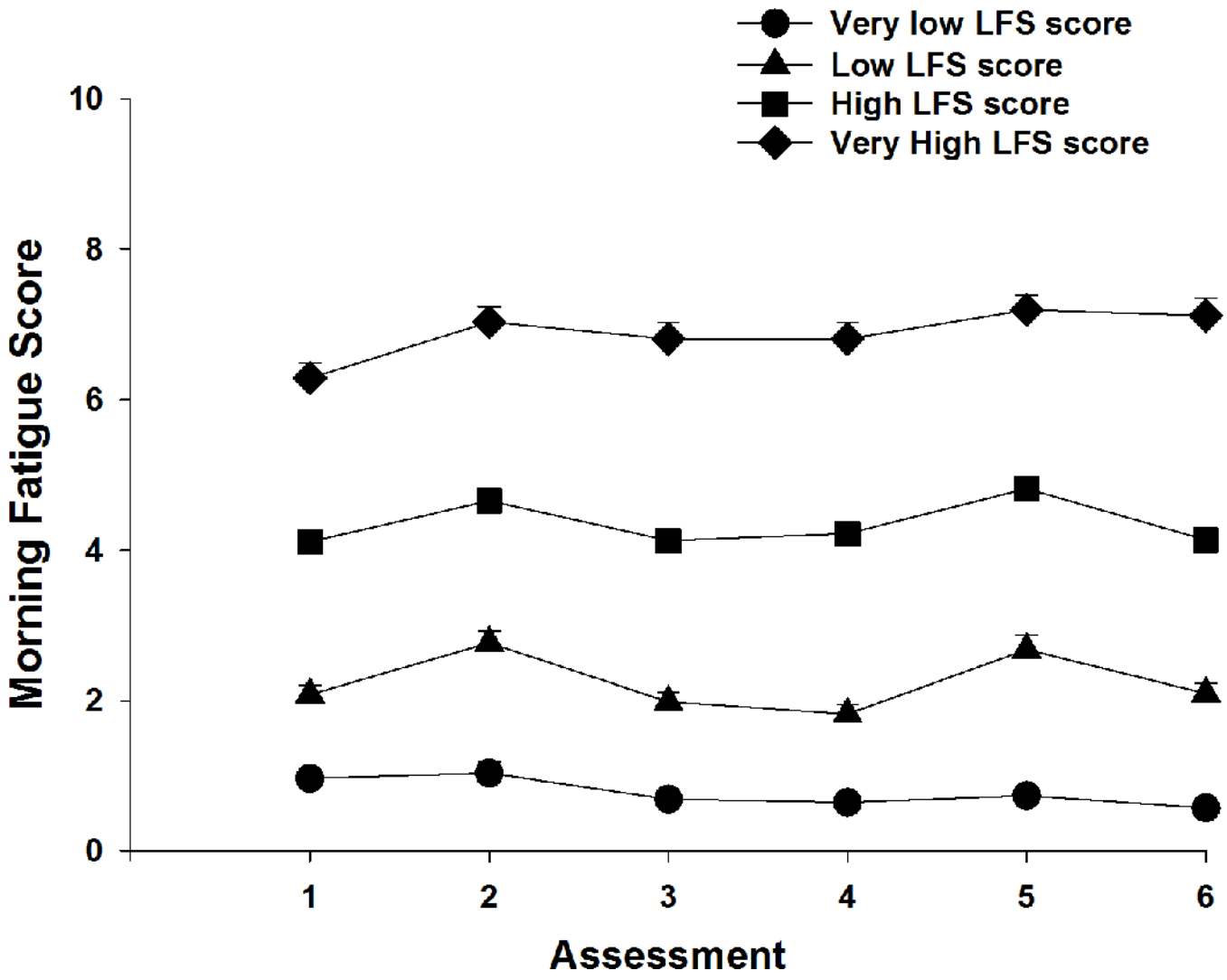

Figure.
Trajectories of morning fatigue for the four latent classes

Table 1

Solutions and Fit Indices for One- Through Five-Classes for Morning Fatigue Latent Profile Scores

Model	LL	AIC	BIC	VMLR	Entropy
1 Class	−13766.38	27574.76	27683.85	n/a	n/a
2 Class	−13034.80	26137.60	26314.23	1463.16[b]	.80
3 Class	−12648.78	25391.56	25635.73	772.04[b]	.80
4 Class[c]	−12481.82	25083.64	25395.35	333.92[a]	.81
5 Class	−12345.67	24837.33	25216.58	272.30[ns]	.83

[ns] Not significant;

[a] p < .01;

[b] p < .001

[c] The 4-class solution was selected because the VLMR was significant, indicating that four classes fit the data better than three classes. In addition, the VLMR was not significant for the 5-class solution, indicating that too many classes had been extracted.

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; LL, log-likelihood; n/a, not applicable; VLMR, Vuong-Lo-Mendell-Rubin likelihood ratio test for the K vs. K-1 model

Table 2

Differences in Demographic and Clinical Characteristics Among the Morning Fatigue Latent Classes

Characteristic	Very Low (0) 261 (19.6%) Mean (SD)	Low (1) 403 (30.2) Mean (SD)	High (2) 528 (39.6%) Mean (SD)	Very High (3) 141 (10.6%) Mean (SD)	Statistics
Age (years)	59.8 (10.9)	58.8 (12.8)	55.3 (12.5)	54.6 (11.5)	F=12.61, p<.001 0 and 1 > 2 and 3
Education (years)	16.1 (3.0)	16.5 (3.1)	16.1 (2.9)	15.8 (3.1)	F=2.01, p=.111
Body mass index (kg/m^2)	25.6 (4.8)	26.0 (5.3)	26.3 (5.8)	27.6 (7.2)	F=4.14, p=.006 0 and 1 < 3
Karnofsky Performance Status score	86.3 (11.3)	83.1 (11.3)	76.9 (11.7)	70.7 (12.1)	F=74.61, p<.001 0>1>2>3
Number of comorbidities	2.1 (1.3)	2.2 (1.3)	2.5 (1.5)	3.0 (1.7)	F=16.39, p<.001 0 and 1 < 2 and 3; 2<3
SCQ score	4.5 (2.6)	5.0 (2.7)	5.9 (3.2)	7.3 (4.3)	F=32.97, p<.001 0 and 1 < 2 and 3; 2<3
AUDIT score	3.1 (2.5)	3.0 (2.2)	3.0 (2.7)	2.6 (2.5)	F=0.70, p=.553
Time since cancer diagnosis (years)	1.9 (3.9)	1.9 (3.8)	2.2 (4.1)	1.6 (2.9)	KW, p=.347
Time since cancer diagnosis (median)	0.43	0.41	0.42	0.45	
Number of prior cancer treatments	1.4 (1.5)	1.5 (1.5)	1.7 (1.5)	1.8 (1.5)	F=2.43, p=.064
Number of metastatic sites including lymph node involvement	1.3 (1.2)	1.2 (1.3)	1.2 (1.2)	1.3 (1.2)	F=0.22, p=.886
Number of metastatic sites excluding lymph node involvement	0.8 (1.0)	0.8 (1.1)	0.8 (1.0)	0.8 (1.1)	F=0.09, p=.968
Hemoglobin (gm/dL)	11.8 (1.4)	11.5 (1.4)	11.5 (1.4)	11.5 (1.5)	F=4.01, p=.007 0 > 1 and 2
Hematocrit (%)	35.4 (4.1)	34.4 (4.2)	34.3 (4.0)	34.4 (4.5)	F=4.68, p=.003 0 > 1 and 2
	% (n)	% (n)	% (n)	% (n)	
Gender					X^2=36.14, p<.001
Female[a]	65.5 (171)	76.4 (308)	83.7 (442)	83.0 (117)	1, 2, and 3 > 0
Male	34.5 (90)	23.3 (94)	16.3 (86)	17.0 (24)	2>1
Transgender[b]	0.0 (0)	0.2 (1)	0.0 (0)	0.0 (0)	
Ethnicity					
White	68.9 (177)	71.5 (286)	69.0 (359)	66.9 (93)	
Black	10.5 (27)	6.3 (25)	6.7 (35)	5.8 (8)	X^2=16.52, p=.057
Asian or Pacific Islander	12.8 (33)	13.0 (52)	12.9 (67)	9.4 (13)	

Characteristic	Very Low (0) 261 (19.6%) Mean (SD)	Low (1) 403 (30.2) Mean (SD)	High (2) 528 (39.6%) Mean (SD)	Very High (3) 141 (10.6%) Mean (SD)	Statistics
Hispanic Mixed or Other	7.8 (20)	9.3 (37)	11.3 (59)	18.0 (25)	
Married or partnered (% yes)	73.9 (190)	68.8 (274)	58.8 (306)	54.7 (76)	X^2=26.33, p<.001 0 and 1 > 2 and 3
Lives alone (% yes)	14.4 (37)	19.0 (76)	23.7 (123)	33.6 (47)	X^2=22.66, p<.001 2 and 3 > 0 3 > 1
Child care responsibilities (% yes)	17.3 (44)	19.5 (77)	25.3 (131)	27.0 (37)	X^2=9.88, p=.020 No significant post hoc contrasts
Care of adult responsibilities (% yes)	7.1 (17)	6.9 (25)	9.0 (43)	7.8 (10)	X^2=1.60, p=.659
Currently employed (% yes)	37.5 (96)	39.1 (156)	33.4 (175)	25.7 (36)	X^2=9.53, p=.023 1>3
Income					
< $30,000+	13.3 (29)	11.9 (43)	20.1 (97)	38.2 (50)	KW, p<.001 3 > 0, 1, and 2 2 > 1
$30,000 to <$70,000	20.6 (45)	21.3 (77)	22.0 (106)	18.3 (24)	
$70,000 to < $100,000	20.2 (44)	14.1 (51)	18.7 (90)	13.0 (17)	
≥ $100,000	45.9 (100)	52.8 (191)	39.2 (189)	30.5 (40)	
Specific comorbidities (% yes)					
Heart disease	5.7 (15)	5.2 (21)	5.9 (31)	5.7 (8)	X^2=0.20, p=.978
High blood pressure	31.4 (82)	31.5 (127)	29.2 (154)	27.7 (39)	X^2=1.21, p=.750
Lung disease	8.0 (21)	9.9 (40)	12.7 (67)	16.3 (23)	X^2=8.05, p=.045 No significant post hoc contrasts
Diabetes	6.9 (18)	7.4 (30)	10.2 (54)	12.8 (18)	X^2=6.01, p=.111
Ulcer or stomach disease	3.1 (8)	5.2 (21)	5.5 (29)	5.0 (7)	X^2=2.38, p=.498
Kidney disease	1.5 (4)	1.0 (4)	1.3 (7)	2.8 (4)	X^2=2.60, p=.458
Liver disease	7.7 (20)	6.2 (25)	6.3 (33)	5.7 (8)	X^2=0.85, p=.837
Anemia or blood disease	9.6 (25)	10.2 (41)	13.1 (69)	19.9 (28)	X^2=11.29, p=.010 3 > 0 and 1
Depression	5.0 (13)	10.9 (44)	25.0 (132)	48.2 (68)	X^2=139.42, p<.001 0<1<2<3
Osteoarthritis	11.9 (31)	11.9 (48)	11.2 (59)	15.6 (22)	X^2=2.08, p=.556
Back pain	18.4 (48)	21.1 (85)	29.2 (154)	39.7 (56)	X^2=29.59, p<.001 0 and 1 < 2 and 3
Rheumatoid arthritis	3.4 (9)	2.0 (8)	2.7 (14)	7.1 (10)	X^2=9.68, p=.022

Characteristic	Very Low (0) 261 (19.6%) Mean (SD)	Low (1) 403 (30.2) Mean (SD)	High (2) 528 (39.6%) Mean (SD)	Very High (3) 141 (10.6%) Mean (SD)	Statistics
					No significant post hoc contrasts
Exercise on a regular basis (% yes)	77.6 (201)	75.6 (298)	68.9 (357)	50.8 (67)	X^2=36.82, p<.001 3 < 0, 1, and 2
Smoking, current or history of (% yes)	30.7 (79)	35.0 (139)	36.2 (187)	41.4 (58)	X^2=4.83, p=.185
Cancer diagnosis					X^2=32.06, p<.001
Breast	31.4 (82)	41.9 (169)	43.8 (231)	40.4 (57)	1 and 2 > 0
Gastrointestinal	44.4 (116)	27.8 (112)	25.6 (135)	29.1 (41)	0 > 1, 2, and 3
Gynecological	13.8 (36)	18.1 (73)	18.6 (98)	18.4 (26)	NS
Lung	10.3 (27)	12.2 (49)	12.1 (64)	12.1 (17)	NS
Type of prior cancer treatment					
No prior treatment	30.8 (77)	26.8 (106)	22.3 (115)	18.2 (25)	
Only surgery, CTX, or RT	38.8 (97)	41.8 (165)	43.6 (225)	43.1 (59)	X^2=14.39, p=.109
Surgery & CTX, or Surgery & RT, or CTX & RT	20.0 (50)	19.0 (75)	20.5 (106)	19.7 (27)	
Surgery & CTX & RT	10.4 (26)	12.4 (49)	13.6 (70)	19.0 (26)	
CTX cycle length					
14 days	46.5 (121)	39.8 (160)	42.1 (222)	38.3 (54)	
21 days	45.8 (126)	51.5 (207)	50.1 (264)	56.7 (80)	X^2=7.77, p=.255
28 days	5.0 (13)	8.7 (35)	7.8 (41)	5.0 (7)	

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; CTX, chemotherapy; gm/dL, grams per deciliter; kg, kilograms; KW, Kruskal Wallis; m^2, meter squared; RT, radiation therapy; SCQ, Self-Administered Comorbidity Questionnaire; SD, standard deviation

[a] Reference group for the post hoc comparisons

[b] Chi Square analysis and post hoc contrasts done without the transgender patient include in the analyses

Table 3

Differences in Symptom Characteristics Among the Morning Fatigue Latent Classes

Characteristic	Very Low (0) 261 (19.6%) Mean (SD)	Low (1) 403 (30.2%) Mean (SD)	High (2) 528 (39.6%) Mean (SD)	Very High (3) 141 (10.6%) Mean (SD)	Statistics
Trait anxiety (≥31.8)[a]	28.4 (6.3)	32.3 (8.7)	38.1 (10.0)	45.4 (11.7)	F=132.88, p<.001 0<1<2<3
State anxiety (≥32.2) [a]	26.7 (7.9)	31.3 (10.7)	36.3 (11.8)	45.7 (14.6)	F=101.09, p<.001 0<1<2<3
Depressive symptoms (≥16) [a]	6.4 (5.6)	9.7 (6.6)	15.6 (9.3)	23.9 (11.5)	F=174.76, p<.001 0<1<2<3
Attentional function (<5.0 low, 5.0 to 7.5 moderate, >7.5 high) [a]	7.8 (1.4)	6.9 (1.5)	5.8 (1.5)	4.6 (1.8)	F=169.75, p<.001 0>1>2>3
Sleep disturbance (≥43) [a]	35.4 (15.6)	46.2 (16.1)	60.0 (16.8)	74.0 (17.2)	F=221.15, p<.001 0<1<2<3
Morning fatigue (≥3.3) [a]	0.9 (0.9)	2.1 (1.4)	4.1 (1.8)	6.5 (1.7)	F=555.09, p<.001 0<1<2<3
Evening fatigue (≥5.6) [a]	3.9 (2.2)	4.8 (2.0)	5.9 (1.7)	7.4 (1.6)	F=122.99, p<.001 0<1<2<3
Morning energy (≤6.2) [a]	5.3 (2.6)	4.5 (2.3)	4.2 (1.8)	3.2 (2.3)	F=31.25, p<.001 0 > 1, 2, and 3; 1 and 2 > 3
Evening energy (≤3.5) [a]	3.8 (2.2)	3.8 (2.0)	3.5 (1.9)	2.5 (2.0)	F=15.61, p<.001 0, 1, and 2 > 3
	% (n)	% (n)	% (n)	% (n)	
Pain					X^2=106.02, p<.001
No pain	39.3 (101)	32.6 (130)	21.8 (112)	10.9 (15)	0 and 1 > 2 and 3; 2<3
Only cancer pain	21.0 (54)	27.3 (109)	29.4 (151)	23.2 (32)	NS
Only non-cancer pain	22.2 (57)	17.0 (68)	12.8 (66)	11.6 (16)	0 > 2
Both cancer and non-cancer pain	17.5 (45)	23.1 (92)	36.0 (185)	54.3 (75)	0 and 1 < 2 and 3; 2<3

[a]= clinically meaningful cutoff score

Abbreviations: NS, not significant; SD, standard deviation

Table 4

Phenotypic Characteristics Associated with Higher Levels of Morning Fatigue

Characteristic	Very High 4 class solution	Very High 3 class solution (Kober et al., 2016a)	HLM Analysis (Wright et al., 2015a)
Demographic Characteristics			
Younger age	◆	◆	◆
Being female	◆	◆	
Ethnicity			◆
Not being married or partnered	◆	◆	
Living alone	◆		
Having a higher income	◆	◆	
Not currently employed	◆		
Clinical Characteristics			
Having a higher BMI	◆		◆
Not exercising regularly	◆	◆	◆
Lower functional status	◆	◆	◆
Having a higher number of comorbidities	◆		
Having a higher SCQ score	◆	◆	
Having a diagnosis of anemia or blood disease	◆	NT	
Having a diagnosis of depression	◆	NT	
Having a diagnosis of lung disease	◆	NT	
Symptom Characteristics			
Higher trait anxiety	◆	NT	
Higher state anxiety	◆	NT	◆
Higher depressive symptoms	◆	NT	◆
Lower attentional function	◆	NT	NT
Higher sleep disturbance	◆	NT	◆
Higher morning fatigue	◆	NT	
Higher evening fatigue	◆	NT	
Lower morning energy	◆	NT	
Lower evening energy	◆	NT	
Having cancer and/or non-cancer pain	◆	NT	

Abbreviations: ◆, association identified; BMI, body mass index; HLM, hierarchical linear modeling; NT, not tested; SCQ, Self-Administered Comorbidity Questionnaire