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Identification of subgroups of chemotherapy patients with distinct sleep disturbance profiles and associated co-occurring symptoms

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Identification of subgroups of chemotherapy patients with distinct sleep disturbance profiles and associated co-occurring symptoms

by
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Dedication

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Abstract

Identification of subgroups of chemotherapy patients with distinct sleep disturbance profiles and associated co-occurring symptoms

by Maria Tejada

Problem: Sleep disturbance is a prevalent symptom that affects up to 88% of oncology patients. It is a significant problem for oncology patients due to its association with increased fatigue, depression and vasomotor/endocrine symptoms; poorer functional status and QOL; and potentially disease progression.

Study Objectives: Study purposes were to identify subgroups of patients with distinct sleep disturbance profiles and to evaluate for differences in demographic, clinical, and various sleep characteristics, as well for differences in the severity of co-occurring symptoms among these subgroups.

Methods: Outpatients with breast, gynecological, gastrointestinal, or lung cancer (n=1331) completed questionnaires six times over two chemotherapy (CTX) cycles. Sleep disturbance was evaluated using the General Sleep Disturbance Scale (GSDS). Latent profile analysis was used to identify distinct subgroups.

Results: Three latent classes with distinct sleep disturbance profiles were identified (Low (25.5%), High (50.8%), Very High (24.0%)). Approximately 75% of the patients had a mean total GSDS score that was above the clinically meaningful cutoff score of ≥43 across all six assessments. Compared to patients in the Low class, patients in High and Very High classes were significantly younger; had a lower functional status; had higher levels of comorbidity; and were more likely to be female, more likely to have childcare responsibilities, less likely to be employed, and less likely to have gastrointestinal cancer. For all of the GSDS subscale and total

scores, significant differences among the latent classes followed the expected pattern (Low<High<Very High). For trait and state anxiety, depressive symptoms, morning and evening fatigue, decrements in attentional function, and decrements in morning and evening energy, significant differences among the latent classes followed the expected pattern (Low<High<Very High).

Conclusions: Clinicians need to perform in-depth assessments of sleep disturbance and co-occurring symptoms to identify high-risk patients and recommend appropriate interventions.

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Introduction

Sleep disturbance is a pervasive symptom that affects 30% to 88% of oncology patients.[1-4] Sleep disturbance is a significant problem for oncology patients due to its association with increased fatigue,[5-7] depression,[8] and vasomotor/endocrine symptoms;[9] poorer functional status[10,11] and quality of life (QOL);[11] and potentially disease progression.[11,12]

While chemotherapy (CTX) is a common and widely used cancer treatment, limited research is available on changes in sleep disturbance during this treatment. In a meta-synthesis of ten cross-sectional and nine longitudinal studies on sleep disturbance in women with breast cancer receiving CTX,[13] findings on sleep disturbance were inconsistent. While some studies found worsening sleep disturbance over time, others did not find significant changes. These discrepancies may be the result of the various instruments used to evaluate sleep disturbance and inconsistencies in the timing of the assessments throughout the continuum of CTX. In addition, several of these studies had small sample sizes, included only patients with breast cancer, and evaluated sleep disturbance at a limited number of time points.

In a more recent longitudinal study that was not included in the meta-synthesis cited above,[14] sleep disturbance was assessed in breast cancer patients at three time points during CTX (i.e., before, after cycle 4, and at one-year post-CTX). Sleep disturbance was measured using actigraphy and the Pittsburg Sleep Quality Index (PSQI). When breast cancer patients were compared to healthy cancer-free women, the breast cancer patients had worse sleep quality at enrollment. Furthermore, in the women with breast cancer, while sleep disturbance worsened at cycle 4, it returned to baseline levels by one-year post-CTX. In another longitudinal study of breast cancer patients,[15] sleep disturbance was assessed using the PSQI at three time points (i.e., 3 to 14 days prior to starting CTX, day 1 of cycle 4, and 6 months after initiation of CTX). While

no significant changes were found over time, patients reported poor sleep quality at all three assessments. Both of these studies had small sample sizes (n=68, [14] n=80 [15]), included only breast cancer patients, and assessed sleep disturbance at a limited number of time points.

In the studies cited above, various objective and subjective measures were used to evaluate sleep disturbance. The PSQI was the most commonly used subjective measure and actigraphy was the most commonly used objective measure. The sleep characteristics assessed in these studies included one or more of the following measures: objective sleep quality, subjective sleep quality, nocturnal sleep characteristics (i.e., nocturnal sleep time, sleep-onset latency, nocturnal awakenings), day sleep time, daytime sleepiness, and insomnia symptoms.[13-15] It is important to note that not all of the aforementioned studies evaluated for all of these sleep disturbance characteristics.

Given that oncology patients receiving CTX rarely experience a single symptom, emerging evidence suggests that an evaluation of the severity of common co-occurring symptoms is warranted.[16-18] For example, in a previous study by our research team, using the Memorial Symptom Assessment Scale (MSAS), a total of 25 symptoms were reported by over 40% of the patients receiving CTX.[19] The five most common co-occurring symptoms out of the 25 were: lack of energy, difficulty sleeping, pain, feeling drowsy, and difficulty concentrating. Of note, this study did not evaluate for the severity of these common co-occurring symptoms.

While a number of studies have reported on the occurrence and deleterious impact of sleep disturbance in oncology patients,[9,10,20] limited information is available on how sleep disturbance changes during CTX; the severity of various sleep disturbance characteristics, and the severity of the most common co-occurring symptoms. Therefore, the purposes of this study were: to identify subgroups of patients with distinct sleep disturbance profiles using latent profile

analysis (LPA) and to evaluate for differences in demographic, clinical, and various sleep characteristics, as well for differences in the severity of common co-occurring symptoms among these subgroups.

Methods

Patients and Settings

This study is part of a longitudinal study, funded by the National Cancer Institute, that evaluated the symptom experience of oncology outpatients receiving CTX.[21-23] Patients were eligible if they: were ≥18 years of age; had a diagnosis of breast, gastrointestinal (GI), gynecological (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 provided written informed consent. Patients were recruited from two Comprehensive Cancer Centers, a Veterans Affairs hospital, and four community-based oncology programs. A total of 2,234 patients were approached and 1,343 consented to participate (60.1% response rate). The major reason for refusal was being too overwhelmed with their cancer treatment. For this study, 1331 patients completed the General Sleep Disturbance Scale (GSDS).

Instruments

Demographic information was obtained using a questionnaire that included age, gender, ethnicity, marital status, living arrangements, education, employment status, child and elder care responsibilities, exercise regularity, and annual income. Patients' self-reported their functional status using the Karnofsky Performance Status (KPS) scale that ranged from 30 (I feel severely disabled and need to be hospitalized) to 100 (I feel normal; I have no complaints or symptoms).[24]

The Self-Administered Comorbidity Questionnaire (SCQ) was used to assess comorbidity. The questionnaire consists of 13 common medical conditions that were simplified into language that could be understood without any prior medical knowledge.[25] It allowed patients to note the severity of a comorbidity by indicating if they had the condition; if they received treatment for it; and if it limited their activities. For each condition, a patient can receive a maximum of 3 points and the total SCQ score ranges from 0 to 39. The SCQ has well-established validity and reliability and has been used in studies of patients with a variety of chronic conditions.[26]

The GSDS consists of 21 items designed to assess the various aspects of sleep disturbance (i.e., quality, quantity, onset latency, mid and early awakenings, sleep medications, daytime sleepines). Each item was rated on a 0 (never) to 7 (everyday) numeric rating scale (NRS). The GSDS total score ranges from 0 (no disturbance) to 147 (extreme sleep disturbance). Each mean subscale score ranges from 0 to 7. Subscale scores of $\geq$3 and a GSDS total score of $\geq$43 indicate a significant level of sleep disturbance that warrants clinical evaluation and management.[27] The GSDS has well-established validity and reliability.[28-30] In this study, the Cronbach's alpha for the GSDS total score was 0.83.

The Spielberger State-Trait Anxiety Inventories (STAI-T and STAI-S) each have 20 items that are rated from 1 to 4. The summed scores for each scale can range from 20 to 80. 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. Cutoff scores of >31.8 and >32.2 indicate high levels of trait and state anxiety, respectively. The STAI-S and STAI-T inventories have well

established validity and reliability.[31-33] In the current study, the Cronbach's alphas for the STAI-T and STAI-S were 0.92 and 0.96, respectively.

The Attentional Function Index (AFI) consists of 16 items designed to measure attentional function.[34] A higher total mean score on a 0 to 10 NRS indicates greater capacity to direct attention. Total scores are grouped into categories of attentional function (i.e., <5.0 low function, 5.0 to 7.5 moderate function, >7.5 high function).[35] The AFI has well established reliability and validity.[34] In this study, the Cronbach's alpha for the total AFI scores was 0.93.

The Center for Epidemiological Studies-Depression scale (CES-D) consists of 20 items selected to represent the major symptoms in the clinical syndrome of depression. A total score can range from 0 to 60, with scores of ≥16 indicating the need for individuals to seek clinical evaluation for major depression. The CES-D has well established validity and reliability.[36-38] In the current study, the Cronbach's alpha for the CES-D total score was 0.89.

The Lee Fatigue Scale (LFS) consists of 18 items designed to assess physical fatigue and energy.[39] Each item was rated on a 0 to 10 NRS. Total fatigue and energy scores were calculated as the mean of the 13 fatigue items and the 5 energy items, 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, 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)[27] and energy (i.e., ≤6.2 for morning energy, ≤3.5 for evening energy). [27] It was chosen for this study because it is relatively short, easy to administer, and has well established validity and reliability.[39-41] In the current 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.

Occurrence of pain was evaluated using the Brief Pain Inventory.[42] Patients who responded yes to the question about having pain were asked to indicate if their pain was or was not related to their cancer treatment. Patients were categorized into one of four groups (i.e., no pain, only noncancer pain, only cancer pain, both cancer and noncancer pain).

Study Procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco and the Institutional Review Board at each of the study sites. Patients were approached by a research staff member in the infusion unit to discuss participation in the study. Written informed consent was obtained from all patients. Given the challenges associated with the recruitment of patients prior to their first cycle of CTX, patients were recruited during their second or third cycle of CTX. Depending on the length of their CTX cycle, patients completed questionnaires in their homes, a total of six times over two cycles of CTX (i.e., prior to CTX administration (i.e., recovery from previous CTX cycle, assessments 1 and 4), approximately 1 week after CTX administration (i.e., acute symptoms, assessments 2 and 5), approximately 2 weeks after CTX administration (i.e., potential nadir, assessments 3 and 6)). Disease and treatment information were collected from medical records.

Data Analysis

Descriptive statistics and frequency distributions were calculated for the demographic and clinical characteristics using Statistical Package for the Social Sciences (SPSS) version 23 (International Business Machines, Armonk, NY). Differences among the latent classes were evaluated using analyses of variance (ANOVA) or Chi Square analyses. The Bonferroni

procedure was used to calculate the post hoc contrasts. A p-value of <.05 was considered statistically significant.

Latent profile analysis (LPA) of sleep disturbance

Unconditional LPA was used to identify the profiles of sleep disturbance means for the total score from the GSDS that characterized unobserved subgroups (i.e., latent classes) of patients over the six assessments. Typically, growth mixture modeling or latent class growth modeling of change trajectories would be used to identify latent classes of individuals who change differently over time. However, the data from this study demonstrated a complex pattern of change because a pre-treatment assessment, an immediate post-treatment assessment, and a second post-treatment assessment were done over two cycles of CTX (i.e., assessments 1, 2, and 3 and assessments 4, 5, and 6). We expected that the trajectory of change for sleep disturbance, measured six times, over two treatment cycles would have a twin peak pattern that looks like "Λ_Λ". Therefore, we identified latent classes of patients based on their profiles of means, where the means were estimated from the GSDS total scores measured on six occasions. In order to incorporate the expected correlations among the repeated measures, we included covariance among GSDS scores that were one or two occasions apart (i.e., a covariance structure with a lag of two). In this way, we retained the within-person correlation among the GSDS scores, at the same time that we focused on the patterns of means that distinguished the latent classes. We limited the covariance structure to a lag of two to accommodate the expected reduction in correlation that would be introduced by two treatments within each set of three measurement occasions, and to reduce model complexity.

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 ("estimator=MLR"). Model fit was evaluated to identify the best solution that characterized the observed latent class structure with the Bayesian Information Criterion (BIC), the Vuong-Lo-Mendell-Rubin likelihood ratio test (VLMR) for the K vs. K-1 model, entropy, and latent class percentages that were large enough to be reliable (i.e., likely to replicate in new samples; 15% or about 85 patients).[43,44] Missing data were accommodated with the use of the Expectation-Maximization (EM) algorithm.[45]

Mixture models, like LPA, are known to produce solutions at local maxima. Therefore, our models were fit with from 1,000 to 2,400 random starts. This approach ensured that the estimated model was replicated many times and was not due to a local maximum. Estimation was done with Mplus Version 7.2. [43]

Results

Latent Classes for Sleep Disturbance

Although the BIC for the four-class solution was lower than the three-class solution, the three-class solution was selected because one of the classes in the four-class solution was too small to be reliable and because the profile of means for two of the classes in the four-class solution did not differ in a meaningful way (i.e., either by profile or mean levels of GSDS total scores; Table 1). In addition, the three-class solution fit better than the two-class solution (lower BIC, VLMR test) and the profiles of means were clinically meaningfully different.

As shown in Figure 1, the trajectories for sleep disturbance scores differed among the latent classes. Because a clinically meaningful total GSDS score for sleep disturbance is ≥43,[27] the sleep disturbance classes were named Low, High, and Very High. For both the Low (25.2%) and the Very High (24.0%) classes, sleep disturbance scores remained relatively constant across the six assessments. In contrast, for the High Sleep Disturbance class (50.8%), sleep disturbance

scores oscillated over the two cycles of CTX, with slightly higher scores reported at assessments 2 and 5 (i.e., the weeks following the administration of CTX).

Differences in Demographic and Clinical Characteristics Among the Sleep Disturbance Classes

Compared to patients in the Low Sleep Disturbance class, patients in the High and Very High classes were significantly younger, had a lower KPS score, and a higher SCQ score (Table 2). Furthermore, compared to the Low Sleep Disturbance class, patients in the High and Very High classes were more likely to be female, less likely to be currently employed, more likely to have childcare responsibilities, and less likely to have a GI cancer diagnosis. In addition, compared to the Low and High Sleep Disturbance classes, patients in the Very High class had a higher body mass index (BMI), were less likely to be married or partnered, were more likely to live alone, and reported a lower annual household income. The remainder of the demographic and clinical characteristics did not differ among the sleep disturbance classes.

Differences in GSDS Subscale Scores Among the Sleep Disturbance Classes

As shown in Table 3, differences were found among the sleep disturbance classes for all of the GSDS subscale scores and total sleep disturbance score at enrollment (all $p<.001$). For all of the subscales of the GSDS (i.e., sleep quality, sleep quantity, sleep onset latency, mid-sleep awakenings, early awakenings, medications for sleep, and excessive daytime sleepiness scores [all $p<.001$]), as well as for the total GSDS score, these significant differences among the three latent classes followed the expected pattern (i.e., Low < High < Very High).

Severity of Co-occurring Symptoms Among the Latent Classes

As shown in Table 4, differences were found among the sleep disturbance classes in the severity scores for all of the co-occurring symptoms at enrollment (all $p<.001$). Trait and state anxiety, depressive symptoms, and morning and evening fatigue scores followed the expected

pattern (i.e., Low < High < Very High). Attentional function, as well as morning and evening energy scores followed the opposite but expected pattern (i.e., Low > High > Very High). In terms of pain, the post hoc contrasts for no pain (i.e., Low > High > Very High) and for having both cancer and non-cancer pain (i.e., Low < High < Very High) were in the expected directions.

Discussion

To our knowledge, this study is the first to use LPA to identify subgroups of patients with distinct sleep disturbance trajectories at six time points over two cycles of CTX. Approximately 75% of the patients had a mean total GSDS score that was above the clinically meaningful cutoff score of ≥43 across all six assessments. Of note, this occurrence rate falls at the higher end of the range of sleep disturbance rates reported in studies of the general oncology population (i.e., 30% to 88%).[1-4] The mean total GSDS score of our patients at enrollment (i.e., 52.5) is above the scores reported by patients at the initiation of radiation therapy (i.e., 44.3 (breast cancer), 34.5 (prostate cancer)[46]) and prior to breast cancer surgery (i.e., 48.1[47]). In addition, the total GSDS scores of our patients were comparable to the scores reported by mothers of a newborn infant (i.e., 55.5[48]) and permanent nightshift workers (i.e., 60.5[29]). While the global GSDS scores among our latent classes were significantly different (Table 3), patients in the Very High class reported higher levels of sleep disturbance (i.e., 74.4) when compared to another latent class analysis of women following breast cancer surgery (i.e., High Sustained class – GSDS score of 58.0[49]). Taken together, these findings suggest that a significant number of patients receiving CTX have very high levels of sleep disturbance for over 6 to 8 weeks.

As shown in Table 3, the GSDS subscale scores provide additional information about the types of sleep disturbance experienced by our three groups of patients. Across all three classes, patients reported insufficient quantity of sleep (i.e., ≥3 days of not getting enough sleep in the

past week). Patients in the High and Very High classes reported significantly poorer quality of sleep and higher scores for the two subscales associated with sleep maintenance (i.e., mid-sleep awakenings, early awakenings). In addition, patients in the Very High class reported higher scores for difficulty initiating sleep (i.e., sleep onset latency) and excessive daytime sleepiness (i.e., 3.8 days out of the week). Consistent with previous studies,[46,47,49] for all three classes, the use of sleep medications was low. Based on these findings, oncology clinicians need to assess patients for sleep disturbance and use a multimodal approach that includes education about sleep hygiene and short-term use of medications to treat this symptom.

In terms of demographic characteristics associated with higher levels of sleep disturbance, our findings are consistent with previous studies that found that younger oncology patients reported higher levels of sleep disturbance.[49-51] In contrast, while some studies found no gender differences,[52,53] others found that female patients reported more sleep disturbance.[54-57] The higher prevalence of sleep disturbance in women may be explained by the concept of a "double work day", where in addition to working a full-time job, women in traditional family roles work a "second-shift" completing household tasks and caring for children.[29] Another potential explanation is the influence of hormonal changes on sleep-wake activity.[58]

While limited data are available to support an association between being married/partnered and worse sleep disturbance, our finding suggests that having a partner who can provide support and assistance during CTX may alleviate some of the stressors that could contribute to sleep disturbance. Similarly, limited research exists to support our finding that unemployment and having a lower household income is associated with worse sleep disturbance. One possible explanation for this finding may be that poorer living conditions and financial

stress associated with these sociodemographic factors can independently predispose an individual to experience sleep disturbance.

In terms of clinical characteristics that differentiated among the latent classes, our findings are consistent with previous studies of patients with heterogenous cancer diagnoses. For example, poorer functional status[10,28,47,49,59-62] and worse comorbidity profiles[47,49] were associated with higher levels of sleep disturbance. Consistent with a previous study of patients who underwent breast cancer surgery,[47] patients with a higher BMI had worse levels of sleep disturbance. While we did not evaluate for obstructive sleep apnea (OSA), this condition is common in patients with a higher BMI. In particular, excessive daytime sleepiness, a cardinal feature of OSA interferes with nocturnal sleep.[63-65]

Furthermore, a relationship exists between a higher BMI and lack of regular exercise,[66] which was associated with higher levels of sleep disturbance in our patients. In terms of clinical implications, the positive impact of exercise on sleep is well studied. In a systematic review of 56 randomized control trials and quasi-randomized controlled trials of cancer patients receiving active treatment,[67] the effects of exercise on QOL outcomes were evaluated. Compared to patients in the non-exercise or usual care groups, patients in the intervention groups had significant reductions in sleep disturbance as well as other QOL outcomes (i.e., anxiety, depression, fatigue, physical functioning, emotional well-being, role function). With regards to a specific cancer diagnosis, limited research is available on the association between GI cancer and the levels of sleep disturbance found in our patients. However, to our knowledge, this study is the first to identify differences in sleep disturbance severity in patients across four different cancer diagnoses.

In terms of the differences in the severity of common co-occurring symptoms among the latent classes, patients who reported higher levels of sleep disturbance also experienced higher levels of physical fatigue, depression, and anxiety and lower levels of energy and decrements in attentional function. Consistent with a previous study of sleep disturbance in women undergoing breast cancer surgery,[49] patients in the Very High class reported symptom severity scores well above the cutoff scores for clinically meaningful levels for all of the co-occurring symptoms mentioned above. Furthermore, confirmed in our study and in previous reports of breast cancer patients,[5,68-71] a positive correlation exists between sleep disturbance and fatigue before CTX. Consistent with another study of breast cancer patients,[72] women who reported higher sleep disturbance experienced decrements in attentional function prior to the initiation of radiation therapy.

In terms of the association between higher sleep disturbance and increased depressive symptoms, our findings are consistent with previous reports of breast cancer patients before,[73] during,[60,71,74] and after[74,75] adjuvant CTX. Similarly, in one study,[76] a relationship was found between disturbed sleep and increased anxiety in women prior to breast cancer surgery. In addition, while limited data are available on the association between the occurrence of pain and sleep disturbance, the occurrence rate for pain of 72.6% in our overall sample is higher than the rate of 59% reported in a systematic review.[77] While we did not evaluate for specific pain conditions, based on the conditions listed on the SCQ, compared to patients in the Low and High classes, patients in the Very High class reported higher rates of back pain. Of note, with the exception of the systematic review of pain,[77] the studies cited above included only breast cancer patients. Additional studies are needed to evaluate the impact of co-occurring symptoms on sleep disturbance in patients receiving CTX.

Limitations

Several limitations need to be acknowledged. Because patients were not recruited prior to the initiation of CTX, changes in sleep disturbance prior to the initiation of treatment were not assessed. Patients in this sample were predominantly White, female, college educated, and had metastatic disease, which suggests that our study sample may not be entirely representative of oncology patients in the United States. While the sample size was very large, which increases the generalizability of the study findings, these patients received a variety of CTX regimens. As a result, differences in sleep disturbance associated with different CTX regimens cannot be evaluated. Lastly, our study included only subjective measures of sleep disturbance. Future studies should include both subjective and objective measures of sleep disturbance.

Conclusions

Despite these limitations, this study is the first to use LPA to identify subgroups of patients with distinct sleep disturbance profiles over two cycles of CTX. In addition, this study is the first to evaluate for differences in the severity of co-occurring symptoms among the sleep disturbance latent classes. This study identified some potentially modifiable demographic (e.g., employment status) and clinical characteristics (e.g., BMI, exercise) associated with a worse sleep disturbance trajectory. Based on these findings, clinicians who care for oncology patients receiving CTX need to perform an in-depth assessment of sleep disturbance and common co-occurring symptoms to identify high-risk patients. In addition, it is important that clinicians educate these patients about sleep hygiene principles and determine whether short term use of sleep medications is needed.

Future longitudinal studies should enroll patients prior to the initiation of CTX and follow them to the completion of CTX. This approach will help confirm the specific latent

classes identified in this study and determine if the severity of sleep disturbance persists throughout the patient's course of CTX. Additional research is needed to evaluate for interactions between common co-occurring symptoms and whether their impact on sleep disturbance trajectories is associated with higher levels of sleep disturbance. Finally, more studies are warranted to evaluate the efficacy of specific interventions to improve sleep throughout the continuum of CTX.

References

1. Davidson JR, MacLean AW, Brundage MD, Schulze K. Sleep disturbance in cancer patients. Soc Sci Med. 2002; 54 (9): 1309-1321.
2. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. J Clin Oncol. 2001; 19 (3): 895-908.
3. Lee K, Cho M, Miaskowski C, Dodd M. Impaired sleep and rhythms in persons with cancer. Sleep medicine reviews. 2004; 8 (3): 199-212.
4. Clark J, Cunningham M, McMillan S, Vena C, Parker K. Sleep-wake disturbances in people with cancer part II: evaluating the evidence for clinical decision making. Oncol Nurs Forum. 2004; 31 (4): 747-771.
5. Liu L, Rissling M, Natarajan L, et al. The longitudinal relationship between fatigue and sleep in breast cancer patients undergoing chemotherapy. Sleep. 2012; 35 (2): 237-245.
6. Ancoli-Israel S, Moore PJ, Jones V. The relationship between fatigue and sleep in cancer patients: a review. Eur J Cancer Care (Engl). 2001; 10 (4): 245-255.
7. Roscoe JA, Kaufman ME, Matteson-Rusby SE, et al. Cancer-related fatigue and sleep disorders. Oncologist. 2007; 12 Suppl 1: 35-42.
8. Accortt EE, Bower JE, Stanton AL, Ganz PA. Depression and vasomotor symptoms in young breast cancer survivors: the mediating role of sleep disturbance. Arch Womens Ment Health. 2015; 18 (3): 565-568.
9. Sephton S, Spiegel D. Circadian disruption in cancer: a neuroendocrine-immune pathway from stress to disease? Brain Behav Immun. 2003; 17 (5): 321-328.
10. Chen ML, Yu CT, Yang CH. Sleep disturbances and quality of life in lung cancer patients undergoing chemotherapy. Lung Cancer. 2008; 62 (3): 391-400.

11. Fortner BV, Stepanski EJ, Wang SC, Kasprowicz S, Durrence HH. Sleep and quality of life in breast cancer patients. J Pain Symptom Manage. 2002; 24 (5): 471-480.

12. Cash E, Sephton SE, Chagpar AB, et al. Circadian disruption and biomarkers of tumor progression in breast cancer patients awaiting surgery. Brain Behav Immun. 2015; 48: 102-114.

13. Enderlin CA, Coleman EA, Cole C, Richards KC, Hutchins LF, Sherman AC. Sleep across chemotherapy treatment: a growing concern for women older than 50 with breast cancer. Oncol Nurs Forum. 2010; 37 (4): 461-A463.

14. 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.

15. Sanford SD, Wagner LI, Beaumont JL, Butt Z, Sweet JJ, Cella D. Longitudinal prospective assessment of sleep quality: before, during, and after adjuvant chemotherapy for breast cancer. Support Care Cancer. 2013; 21 (4): 959-967.

16. Miaskowski C, Barsevick A, Berger A, et al. Advancing Symptom Science Through Symptom Cluster Research: Expert Panel Proceedings and Recommendations. J Natl Cancer Inst. 2017; 109 (4).

17. Miaskowski C. Future Directions in Symptom Cluster Research. Semin Oncol Nurs. 2016; 32 (4): 405-415.

18. Tantoy IY, Cataldo JK, Aouizerat BE, Dhruva A, Miaskowski C. A Review of the Literature on Multiple Co-occurring Symptoms in Patients With Colorectal Cancer Who Received Chemotherapy Alone or Chemotherapy With Targeted Therapies. Cancer Nurs. 2016; 39 (6): 437-445.

19. Miaskowski C, Cooper BA, Melisko M, et al. Disease and treatment characteristics do not predict symptom occurrence profiles in oncology outpatients receiving chemotherapy. Cancer. 2014; 120 (15): 2371-2378.

20. Carney S, Koetters T, Cho M, et al. Differences in sleep disturbance parameters between oncology outpatients and their family caregivers. J Clin Oncol. 2011; 29 (8): 1001-1006.

21. Papachristou N, Barnaghi P, Cooper BA, et al. Congruence Between Latent Class and K-Modes Analyses in the Identification of Oncology Patients With Distinct Symptom Experiences. J Pain Symptom Manage. 2018; 55 (2): 318-333.e314.

22. Miaskowski C, Cooper BA, Aouizerat B, et al. The symptom phenotype of oncology outpatients remains relatively stable from prior to through 1 week following chemotherapy. Eur J Cancer Care (Engl). 2017; 26 (3).

23. Miaskowski C, Dunn L, Ritchie C, et al. Latent Class Analysis Reveals Distinct Subgroups of Patients Based on Symptom Occurrence and Demographic and Clinical Characteristics. J Pain Symptom Manage. 2015; 50 (1): 28-37.

24. Karnofsky D. Performance scale. New York: Plenum Press; 1977.

25. 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.

26. Brunner F, Bachmann LM, Weber U, et al. Complex regional pain syndrome 1--the Swiss cohort study. BMC Musculoskelet Disord. 2008; 9: 92.

27. Fletcher BS, Paul SM, Dodd MJ, et al. Prevalence, severity, and impact of symptoms on female family caregivers of patients at the initiation of radiation therapy for prostate cancer. J Clin Oncol. 2008; 26 (4): 599-605.

28. Miaskowski C, Lee KA. Pain, fatigue, and sleep disturbances in oncology outpatients receiving radiation therapy for bone metastasis: a pilot study. J Pain Symptom Manage. 1999; 17 (5): 320-332.

29. Lee KA. Self-reported sleep disturbances in employed women. Sleep. 1992; 15 (6): 493-498.

30. Lee KA, DeJoseph JF. Sleep disturbances, vitality, and fatigue among a select group of employed childbearing women. Birth. 1992; 19 (4): 208-213.

31. Kennedy BL, Schwab JJ, Morris RL, Beldia G. Assessment of state and trait anxiety in subjects with anxiety and depressive disorders. Psychiatr Q. 2001; 72 (3): 263-276.

32. 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.

33. Bieling PJ, Antony MM, Swinson RP. The State-Trait Anxiety Inventory, Trait version: structure and content re-examined. Behav Res Ther. 1998; 36 (7-8): 777-788.

34. Cimprich B, Visovatti M, Ronis DL. The Attentional Function Index--a self-report cognitive measure. Psychooncology. 2011; 20 (2): 194-202.

35. Cimprich B, So H, Ronis DL, Trask C. Pre-treatment factors related to cognitive functioning in women newly diagnosed with breast cancer. Psychooncology. 2005; 14 (1): 70-78.

36. 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.

37. Sheehan TJ, Fifield J, Reisine S, Tennen H. The measurement structure of the Center for Epidemiologic Studies Depression Scale. J Pers Assess. 1995; 64 (3): 507-521.

38. Carpenter JS, Andrykowski MA, Wilson J, et al. Psychometrics for two short forms of the Center for Epidemiologic Studies-Depression Scale. Issues Ment Health Nurs. 1998; 19 (5): 481-494.

39. Lee KA, Hicks G, Nino-Murcia G. Validity and reliability of a scale to assess fatigue. Psychiatry Res. 1991; 36 (3): 291-298.

40. 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.

41. 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.

42. 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.

43. Muthen LK, Muthen BO. Mplus User's Guide (8th ed.). 8th ed. Los Angeles, CA: Muthen & Muthen; 1998-2017.

44. 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.

45. Muthen B, Shedden K. Finite mixture modeling with mixture outcomes using the EM algorithm. Biometrics. 1999; 55 (2): 463-469.

46. Garrett K, Dhruva A, Koetters T, et al. Differences in sleep disturbance and fatigue between patients with breast and prostate cancer at the initiation of radiation therapy. J Pain Symptom Manage. 2011; 42 (2): 239-250.

47. Van Onselen C, Paul SM, Lee K, et al. Trajectories of sleep disturbance and daytime sleepiness in women before and after surgery for breast cancer. J Pain Symptom Manage. 2013; 45 (2): 244-260.

48. Gay CL, Lee KA, Lee SY. Sleep patterns and fatigue in new mothers and fathers. Biol Res Nurs. 2004; 5 (4): 311-318.

49. Van Onselen C, Cooper BA, Lee K, et al. Identification of distinct subgroups of breast cancer patients based on self-reported changes in sleep disturbance. Support Care Cancer. 2012; 20 (10): 2611-2619.

50. Miaskowski C, Cooper BA, Paul SM, et al. Subgroups of patients with cancer with different symptom experiences and quality-of-life outcomes: a cluster analysis. Oncol Nurs Forum. 2006; 33 (5): E79-89.

51. Pud D, Ben Ami S, Cooper BA, et al. The symptom experience of oncology outpatients has a different impact on quality-of-life outcomes. J Pain Symptom Manage. 2008; 35 (2): 162-170.

52. Baldwin CM, Kapur VK, Holberg CJ, Rosen C, Nieto FJ, Sleep Heart Health Study G. Associations between gender and measures of daytime somnolence in the Sleep Heart Health Study. Sleep. 2004; 27 (2): 305-311.

53. Sanford SD, Lichstein KL, Durrence HH, Riedel BW, Taylor DJ, Bush AJ. The influence of age, gender, ethnicity, and insomnia on Epworth sleepiness scores: a normative US population. Sleep Med. 2006; 7 (4): 319-326.

54. Baldwin CM, Grant M, Wendel C, et al. Gender differences in sleep disruption and fatigue on quality of life among persons with ostomies. J Clin Sleep Med. 2009; 5 (4): 335-343.

55. Krishnan V, Collop NA. Gender differences in sleep disorders. Curr Opin Pulm Med. 2006; 12 (6): 383-389.

56. Foster SN, Hansen SL, Capener DC, Matsangas P, Mysliwiec V. Gender differences in sleep disorders in the US military. Sleep Health. 2017; 3 (5): 336-341.

57. Buysse DJ, Hall ML, Strollo PJ, et al. Relationships between the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and clinical/polysomnographic measures in a community sample. J Clin Sleep Med. 2008; 4 (6): 563-571.

58. Dzaja A, Arber S, Hislop J, et al. Women's sleep in health and disease. J Psychiatr Res. 2005; 39 (1): 55-76.

59. Beck SL, Berger AM, Barsevick AM, Wong B, Stewart KA, Dudley WN. Sleep quality after initial chemotherapy for breast cancer. Support Care Cancer. 2010; 18 (6): 679-689.

60. Colagiuri B, Christensen S, Jensen AB, Price MA, Butow PN, Zachariae R. Prevalence and predictors of sleep difficulty in a national cohort of women with primary breast cancer three to four months postsurgery. J Pain Symptom Manage. 2011; 42 (5): 710-720.

61. Dodd MJ, Cho MH, Cooper BA, et al. Identification of latent classes in patients who are receiving biotherapy based on symptom experience and its effect on functional status and quality of life. Oncol Nurs Forum. 2011; 38 (1): 33-42.

62. Dodd MJ, Cho MH, Cooper BA, Miaskowski C. The effect of symptom clusters on functional status and quality of life in women with breast cancer. Eur J Oncol Nurs. 2010; 14 (2): 101-110.

63. Seneviratne U, Puvanendran K. Excessive daytime sleepiness in obstructive sleep apnea: prevalence, severity, and predictors. Sleep Med. 2004; 5 (4): 339-343.

64. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med. 2002; 165 (9): 1217-1239.

65. Dostalova S, Susta M, Vorlova T, Sonka K. Sleepiness in patients with obstructive sleep apnoea - daytime course and impact of nocturnal respiratory events. Neuro Endocrinol Lett. 2012; 33 (7): 684-688.

66. Wareham NJ, van Sluijs EM, Ekelund U. Physical activity and obesity prevention: a review of the current evidence. Proc Nutr Soc. 2005; 64 (2): 229-247.

67. Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, Topaloglu O. Exercise interventions on health-related quality of life for people with cancer during active treatment. Cochrane Database Syst Rev. 2012; 8: CD008465.

68. Vargas S, Wohlgemuth WK, Antoni MH, Lechner SC, Holley HA, Carver CS. Sleep dysfunction and psychosocial adaptation among women undergoing treatment for non-metastatic breast cancer. Psychooncology. 2010; 19 (6): 669-673.

69. Berger AM, Farr L. The influence of daytime inactivity and nighttime restlessness on cancer-related fatigue. Oncol Nurs Forum. 1999; 26 (10): 1663-1671.

70. Jacobsen PB, Hann DM, Azzarello LM, Horton J, Balducci L, Lyman GH. Fatigue in women receiving adjuvant chemotherapy for breast cancer: characteristics, course, and correlates. J Pain Symptom Manage. 1999; 18 (4): 233-242.

71. Kim HJ, Barsevick AM, Tulman L, McDermott PA. Treatment-related symptom clusters in breast cancer: a secondary analysis. J Pain Symptom Manage. 2008; 36 (5): 468-479.

72. Merriman JD, Dodd M, Lee K, et al. Differences in self-reported attentional fatigue between patients with breast and prostate cancer at the initiation of radiation therapy. Cancer Nurs. 2011; 34 (5): 345-353.

73. Ancoli-Israel S, Liu L, Marler MR, et al. Fatigue, sleep, and circadian rhythms prior to chemotherapy for breast cancer. Support Care Cancer. 2006; 14 (3): 201-209.

74. Thomas KS, Bower J, Hoyt MA, Sepah S. Disrupted sleep in breast and prostate cancer patients undergoing radiation therapy: the role of coping processes. Psychooncology. 2010; 19 (7): 767-776.

75. Couzi RJ, Helzlsouer KJ, Fetting JH. Prevalence of menopausal symptoms among women with a history of breast cancer and attitudes toward estrogen replacement therapy. J Clin Oncol. 1995; 13 (11): 2737-2744.

76. Wright CE, Schnur JB, Montgomery GH, Bovbjerg DH. Psychological factors associated with poor sleep prior to breast surgery: an exploratory study. Behav Med. 2010; 36 (3): 85-91.

77. van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. Ann Oncol. 2007; 18 (9): 1437-1449.

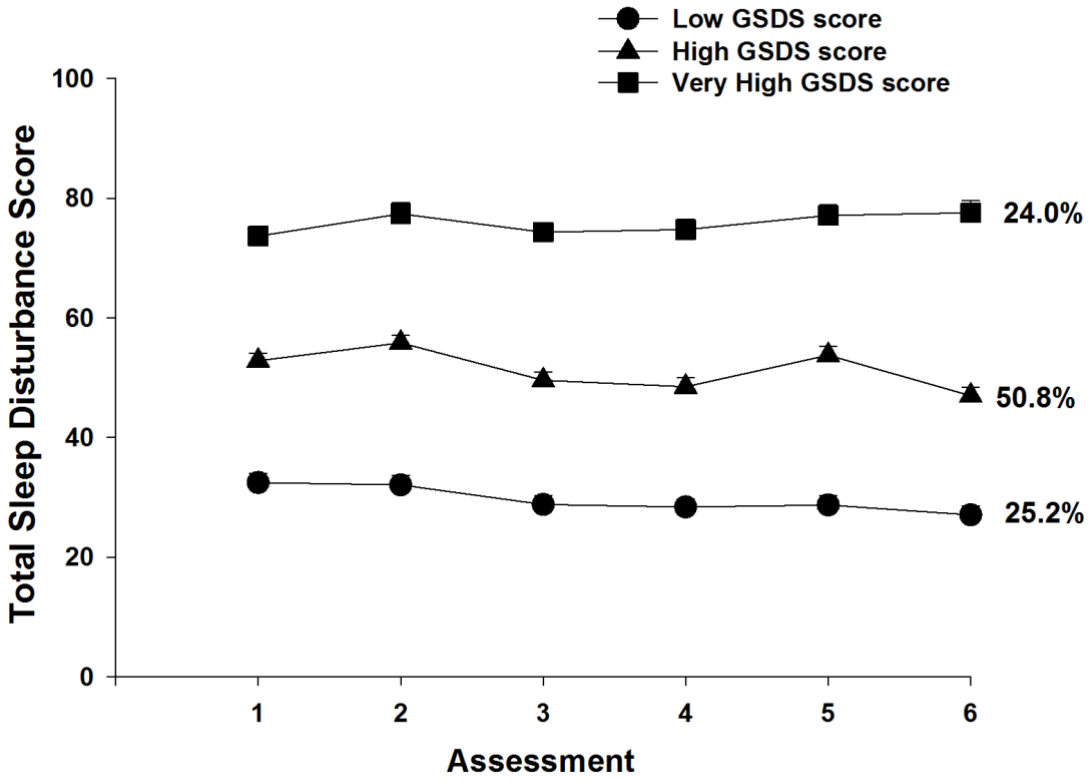

Figure 1. Changes in Sleep Disturbance trajectories for the three latent classes over six time points

Table 1 – General Sleep Disturbance Latent Profile Solutions and Fit Indices for One- Through Four-Class Solutions

Model	LL	AIC	BIC	Entropy	VLMR
1 Class	-28080.06	56208.12	56332.77	n/a	n/a
2 Class	-27692.33	55458.66	55650.83	.70	775.46****
3 Class[a]	-27447.03	54994.05	55253.74	.73	490.61****
4 Class	-27323.81	54773.63	55100.83	.68	46.43*

[na] Baseline LL, not applicable for one class; * p < .05; **** p < .0001

[a] The three class solution was selected because the BIC for this solution was lower than the BIC for the 2-class solution. In addition, although the BIC was lower for the 4-class solution, two classes in the 4-class solution were not clinically different and had similar profiles. Therefore, the 3-class solution was selected because it fit better than the 2-class solution, identified three clinically different profiles, and was more parsimonious than the 4-class solution. In addition, the VLMR was significant for the 3-class solution, indicating that three classes fit the data better than two classes, and entropy was larger for the 3-class compared to the 4-class solution.

Abbreviations: AIC = Akaike's Information Criterion; BIC = Bayesian Information Criterion; LL = log-likelihood; 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 Sleep Disturbance Latent Classes (n=1331)

Characteristic	Low GSDS score (1) n=336 (25.2%)	High GSDS score (2) n=676 (50.8%)	Very High GSDS score (3) n=319 (24.0%)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	59.8 (11.6)	56.6 (12.7)	55.4 (11.9)	F=11.84, p<.001 1>2 and 3
Education (years)	16.2 (3.0)	16.2 (3.0)	16.1 (3.1)	F=0.21, p=.810
Body mass index (kg/m^2)	25.7 (4.8)	25.9 (5.6)	27.2 (6.4)	F=7.11, p=.001 1 and 2<3
Karnofsky Performance Status score	86.4 (11.0)	79.4 (12.0)	74.6 (12.2)	F=81.51, p<.001 1>2>3
Self-administered Comorbidity Questionnaire score	4.5 (2.5)	5.4 (3.1)	6.7 (3.7)	F=43.43, p<.001 1<2<3
Time since diagnosis (years)	2.0 (3.5)	2.0 (4.1)	1.8 (3.7)	KW, p=.964
Time since diagnosis (median; years)	0.42	0.42	0.42	
Number of prior cancer treatments	1.6 (1.6)	1.6 (1.5)	1.6 (1.4)	F=0.178, p=.837
Number of metastatic sites including lymph node involvement [a]	1.4 (1.3)	1.2 (1.2)	1.2 (1.2)	F=2.46, p=.086
Number of metastatic sites excluding lymph node involvement	0.9 (1.1)	0.8 (1.0)	0.7 (1.0)	F=2.56, p=.078
Hemoglobin	11.7 (1.5)	11.5 (1.4)	11.6 (1.4)	F=2.22, p=.109
Hematocrit	35.0 (4.3)	34.4 (4.1)	34.6 (4.0)	F=2.21,p=.110
	% (n)	% (n)	% (n)	
Gender (% female)	66.0 (221)	81.8 (553)	82.4 (263)	X^2=37.59, p<.001 1<2 and 3
Self-reported ethnicity				X^2=8.90, p=.179
White	66.4 (221)	70.4 (468)	71.2 (225)	
Asian or Pacific Islander	14.4 (48)	12.9 (86)	9.5 (30)	
Black	9.6 (32)	6.2 (41)	7.0 (22)	
Hispanic, Mixed, or Other	9.6 (32)	10.5 (70)	12.3 (39)	
Married or partnered (% yes)	71.0 (235)	65.1 (435)	56.2 (176)	X^2=15.56, p<.001 1 and 2>3
Lives alone (% yes)	17.2 (57)	20.2 (135)	29.0 (91)	X^2=14.63, p=.001 1 and 2<3
Currently employed (% yes)	42.8 (142)	34.8 (233)	27.3 (86)	X^2=17.03, p<.001 1 > 2 and 3
Annual household income				KW=14.15, p<.001 1 and 2>3
Less than $30,000	13.6 (39)	15.2 (93)	30.0 (88)	
$30,000 to $70,000	22.3 (64)	22.6 (138)	17.1 (50)	
$70,000 to $100,000	17.1 (49)	18.2 (111)	14.0 (41)	
Greater than $100,000	47.0 (135)	44.0 (269)	38.9 (114)	
Child care responsibilities (% yes)	16.2 (53)	22.1 (146)	28.8 (90)	X^2=14.59, p=.001 1<3

Elder care responsibilities (% yes)	5.2 (16)	9.6 (58)	7.5 (22)	X^2=5.42, p=.067
Exercise on a regular basis (% yes)	76.7 (257)	71.8 (472)	62.1 (192)	X^2=17.23, p<.001 1 and 2>3
Cancer diagnosis				X^2=15.14, p=.019
Breast cancer	35.7 (120)	41.3 (279)	43.3 (138)	NS
Gastrointestinal cancer	38.4 (129)	28.3 (191)	26.6 (85)	1>2 and 3
Gynecological cancer	14.3 (48)	18.2 (123)	19.1 (61)	NS
Lung cancer	11.6 (39)	12.3 (83)	11.0 (35)	NS
Prior cancer treatment				
No prior treatment	29.7 (97)	24.5 (161)	21.4 (67)	
Only surgery, CTX, or RT	37.9 (124)	42.9 (282)	44.1 (138)	X^2=7.59, p=.270
Surgery and CTX, or surgery and RT, or CTX and RT	20.5 (67)	19.6 (129)	19.5 (61)	
Surgery and CTX and RT	11.9 (39)	12.9 (85)	15.0 (47)	
Metastatic sites				
No metastasis	27.3 (91)	33.3 (223)	36.1 (113)	
Only lymph node metastasis	20.4 (68)	22.9 (153)	21.4 (67)	X^2=9.65, p=.140
Only metastatic disease in other sites	25.2 (84)	19.7 (132)	19.8 (62)	
Metastatic disease in lymph nodes and other sites	27.0 (90)	24.1 (161)	22.7 (71)	
Cycle length				
14 day cycle	45.2 (152)	39.5 (267)	43.0 (136)	X^2=4.12, p=.390
21 day cycle	47.3 (159)	52.8 (357)	50.9 (161)	
28 day cycle	7.4 (25)	7.7 (52)	6.0 (19)	

[a]Total number of metastatic sites evaluated was 9.

Abbreviations: CTX = chemotherapy, GSDS = General Sleep Disturbance Scale, kg = kilograms, KW = Kruskal Wallis, m^2 = meters squared, NS = not significant, RT = radiation therapy, SD = standard deviation

Table 3 – Differences Subscale Scores for the General Sleep Disturbance Scale at Enrollment (n=1331)

Subscales for the General Sleep Disturbance Scale	Low GSDS score (1) n=336 (25.2%)	High GSDS score (2) n=676 (50.8%)	Very High GSDS score (3) n=319 (24.0%)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Quality of sleep	1.8 (1.3)	3.3 (1.5)	4.9 (1.4)	F=378.20, p<.001 1<2<3
Quantity of sleep	3.8 (1.3)	4.6 (1.5)	5.5 (1.5)	F=116.20, p<.001 1<2<3
Sleep onset latency	1.2 (1.3)	2.6 (2.0)	4.6 (2.2)	F=243.66, p<.001 1<2<3
Mid-sleep awakenings	3.8 (2.5)	4.9 (2.1)	6.1 (1.4)	F=99.84, p<.001 1<2<3
Early awakenings	1.9 (2.0)	3.6 (2.3)	5.3 (2.0)	F=194.11, p<.001 1<2<3
Medications for sleep	0.2 (0.4)	0.6 (0.7)	1.1 (1.0)	F=97.34, p<.001 1<2<3
Excessive daytime sleepiness	1.4 (1.0)	2.7 (1.3)	3.8 (1.2)	F=305.63, p<.001 1<2<3
Total GSDS Score	31.4 (10.8)	52.6 (14.7)	74.4 (13.6)	F=792.25, p<.001 1<2<3

Abbreviation: GSDS = General Sleep Disturbance Scale, SD = standard deviation

Table 4 – Severity of Common Symptoms Among the Latent Classes at Enrollment (n=1331)

Instrument*	Low GSDS score (1) (25.2%) n=336	High GSDS score (2) (50.8%) n=676	Very High GSDS score (3) (24.0%) n=319	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
STAI-T ≥31.8	29.2 (7.4)	34.9 (9.3)	41.9 (11.6)	F=140.22, p<.001 1<2<3
STAI-S ≥32.2	27.7 (8.4)	33.4 (11.3)	41.5 (13.9)	F=118.57, p<.001 1<2<3
AFI >7.5	7.5 (1.5)	6.3 (1.7)	5.4 (1.8)	F=134.48, p<.001 1>2>3
CES-D ≥16	6.6 (5.6)	12.7 (8.3)	19.8 (11.3)	F=189.45, p<.001 1<2<3
LFS morning fatigue ≥3.2	1.6 (1.5)	3.1 (2.1)	4.8 (2.1)	F=222.14, p<.001 1<2<3
LFS evening fatigue ≥5.6	4.1 (2.1)	5.5 (2.0)	6.3 (1.8)	F=106.64, p<.001 1<2<3
LFS morning energy ≤6.2	5.1 (2.4)	4.3 (2.2)	3.9 (1.9)	F=24.08, p<.001 1>2>3
LFS evening energy ≤3.5	4.1 (2.0)	3.5 (2.0)	3.2 (2.1)	F=15.80, p<.001 1>2>3
	% (n)	% (n)	% (n)	
Pain Type				X^2=103.29, p<.001
No pain	40.2 (133)	26.8 (177)	15.2 (48)	1>2>3
Only non-cancer pain	20.5 (68)	15.2 (100)	12.4 (39)	1>3
Only cancer pain	20.8 (69)	30.2 (199)	23.8 (75)	1<2
Both cancer and non-cancer pain	18.4 (61)	27.9 (184)	48.6 (153)	1<2<3

*Values below the instrument indicate clinically meaningful cut point scores.

Abbreviations: Attentional Function Index = AFI; Center for Epidemiological Studies-Depression scale = CES-D; Lee Fatigue Scale = LFS; Spielberger State Anxiety Inventory = STAI-S; Spielberger Trait Anxiety Inventory = STAI-T; SD = standard deviation.

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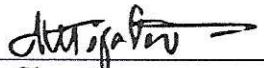

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