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Oncology Outpatients with Worse Anxiety AND Sleep Disturbance Profiles Are at Increased Risk for a Higher Symptom Burden and Poorer Quality of Life

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Abstract

Background: Anxiety and sleep disturbance are frequent symptoms during chemotherapy.

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Objectives: Purposes were to identify subgroups of oncology outpatients with distinct joint anxiety AND sleep disturbance profiles, as well as evaluate for differences in demographic and clinical characteristics, sleep disturbance characteristics, severity of common symptoms, and quality of life outcomes among these subgroups.

Methods: Oncology outpatients (n=1331) completed self-report measures of anxiety and sleep disturbance six times over two chemotherapy cycles. Latent profile analysis was done to identify subgroups of patients with distinct joint anxiety and sleep disturbance profiles.

Results: Three profiles were identified (i.e., no anxiety and low sleep disturbance (59.7%); moderate anxiety and high sleep disturbance (32.5%); high anxiety and very high sleep disturbance (7.8%)). Compared to the no anxiety and low sleep disturbance class, the other two classes were younger; less likely to be married; had a lower annual household income; and had childcare responsibilities. Patients in the two worse profiles had problems with both sleep initiation and maintenance. These patients reported higher levels of depressive symptoms, trait and state anxiety, and evening fatigue as well as lower levels of morning and evening energy, cognitive function, and poorer quality of life.

Conclusions: Over 40% of patients had moderate or high levels of anxiety AND high or very high levels of sleep disturbance. Modifiable risk factors associated with these profiles may be used to develop targeted interventions for one or both symptoms.

Implications for Practice: Clinicians need to assess for the co-occurrence of anxiety and sleep disturbance.

Keywords

anxiety; sleep disturbance; chemotherapy; cancer; latent profile analysis

Introduction

Chemotherapy is an essential component of cancer treatment.[1] Each year, in the United States, ~650,000 individuals receive chemotherapy.[2] While numerous approaches are used to mitigate the adverse effects of chemotherapy, pervasive symptoms compromise patients' functional status, life expectancy, and quality of life (QOL).[3-5] In addition, these unrelieved symptoms can have a negative effect on treatment adherence[5] and decision-making.[6] Anxiety and sleep disturbance are two symptoms that often co-occur during chemotherapy.[7-9] Given the large number of patients who undergo chemotherapy, information is needed on modifiable risk factors for anxiety and sleep disturbance as individual symptoms, as well as risk factors associated with the co-occurrence of these two symptoms.

As noted in three systematic reviews,[10-12] 16.8% to 41.9% of oncology patients experience anxiety. Unrelieved anxiety has negative effects on treatment outcomes,[13] overall survival,[5, 10] functional status,[10] and QOL.[11] While a number of longitudinal studies have evaluated for changes in anxiety in patients undergoing chemotherapy,[5, 6, 14-16] only three[5, 14, 15] used a person-centered analytic approach to identify groups of patients with distinct anxiety profiles.

In the first study of patients with advanced breast cancer,[14] anxiety was assessed using the Hospital Anxiety and Depression Scale (HADS) before the first cycle of adjuvant chemotherapy and again after 1.5, 3, 6, and 12 months. Using latent growth mixture modeling (LGMM), four classes were identified (i.e., low-stable, delayed, recovering, high-stable). While no demographic or clinical characteristics were associated with latent class membership, patients in the delayed, recovering, and high-stable classes had higher physical symptom distress, as well as higher levels of rumination and lower levels of optimism.

In the second study,[5] anxiety was evaluated daily using a single dichotomous item during cycles two and three of chemotherapy. Using LGMM, 46.7% of the women with breast cancer reported anxiety during cycle two and 39.7% during cycle three. Two distinct anxiety profiles (i.e., consistently mild during cycles two and three, consistently moderate during cycle two) were identified. Membership in the consistently moderate class was associated with receiving doxorubicin, not having a college education, or spending more hours a day lying down.

Most recently, we used latent profile analysis (LPA) to evaluate for distinct anxiety profiles in a sample of oncology outpatients over two cycles of chemotherapy.[15] State anxiety was evaluated using the Spielberger State Anxiety Inventory (STAI-S). Four distinct anxiety profiles were identified (i.e., Low, Moderate, High, Very High). Compared to the Low class, membership in the other three classes was associated with younger age; Hispanic ethnicity; lower functional status; and a higher number of comorbidities. In addition, these patients reported higher levels of evening fatigue; less morning energy; less evening energy; lower cognitive function; and occurrence of both non-cancer and cancer-related pain.

While the studies cited above provide useful information, some limitations warrant consideration. While a person-centered analytic approach was used to identify distinct anxiety profiles, the first two studies included only women with breast cancer. In addition, various instruments were used to measure anxiety (i.e., HADS,[14] STAI-S,[15] dichotomous measure[5]). Finally, while all the studies reported on risk factors for anxiety, only one study[15] noted that higher levels of common symptoms (e.g., fatigue) were associated with a worst anxiety profile.

While less well studied than anxiety, sleep disturbance is a significant problem in patients receiving chemotherapy.[17, 18] Present in up to 88% of these patients,[17-21] clinically meaningful levels of sleep disturbance are associated with decreases in immunologic responses,[20] increases in inflammation,[20, 21] increases in emotional problems,[19-21] decrements in QOL,[19, 20] and higher mortality rates.[19, 21] In a meta-synthesis of 19 studies of older women with breast cancer undergoing chemotherapy,[18] poor subjective and objective sleep quality was reported during the active and recovery stages of the treatment. Furthermore, nocturnal awakenings, insomnia, and decreased sleep quality were reported as frequent occurrences prior to and during the first three cycles of chemotherapy. However, these findings must be interpreted with caution because although sleep disturbance was evaluated at different points during chemotherapy, it was limited to the first few cycles rather than across the entire treatment. In addition, most sample sizes were small, and a variety of subjective and objective measures were used to evaluate various aspects of sleep disturbance.

To date, only two longitudinal studies have evaluated for distinct sleep disturbance profiles in patients receiving chemotherapy.[17, 22] In the first study of women with breast cancer,[22] two distinct sleep disturbance classes (i.e., mild decreasing, moderate increasing) were identified using LGMM. Sleep disturbance was evaluated with a single dichotomous (yes/no) item during cycles two and three of chemotherapy. While the severity of sleep disturbance worsened as the chemotherapy treatment progressed, no demographic or clinical characteristics were associated with class membership. In the second study by our research team,[17] LPA was used to identify three subgroups of patients with distinct sleep disturbance profiles (i.e., Low, High, Very High). Compared to the Low class, patients in the High and Very High classes were younger; more likely to be female; had a lower functional status; had higher levels of comorbidity; were more likely to have child care responsibilities; less likely to be employed; and less likely to have gastrointestinal cancer. For the General Sleep Disturbance Scale (GSDS) subscales (i.e., quality, quantity, onset latency, mid and early awakenings, sleep medications, daytime sleepiness) and total scores, significant differences were found among the latent classes that followed the same pattern (Low < High < Very High). In addition, for trait and state anxiety, depressive symptoms, morning and evening fatigue, decrements in cognitive function, and decrements in morning and evening energy scores, significant differences among the latent classes followed the same pattern (Low < High < Very High).

Given that emerging evidence suggests an association between anxiety and sleep disturbance in patients undergoing chemotherapy [7-9] and the paucity of research on the evaluation of these two symptoms together, the purpose of this study was to identify subgroups of patients with distinct joint anxiety AND sleep disturbance profiles. Once these profiles were identified, we evaluated for differences in demographic and clinical characteristics, sleep disturbance characteristics, severity of common symptoms, and QOL outcomes among the subgroups. This analysis builds on our previous LPA analyses that identified subgroups of patients undergoing chemotherapy with distinct anxiety[15] and sleep disturbance[17] profiles.

Methods

Patients and Settings

This study is part of a larger, longitudinal study of the symptom experience of oncology outpatients receiving chemotherapy[23] that was guided by the Theory of Symptom Management.[24] Briefly, patients were ≥18 years of age; had a diagnosis of breast, gastrointestinal, gynecological, or lung cancer; had received chemotherapy within the preceding four weeks; were scheduled to receive at least two additional cycles of chemotherapy; were able to read, write, and understand English; and provided written informed consent. Patients were recruited from two comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs.

Study Procedures

The study was approved by the Institutional Review Board at each of the study sites. Of the 2234 patients approached, 1343 (60.1%) consented to participate. The major reason for refusal was being too overwhelmed with their cancer treatments. These patients

completed questionnaires, a total of six times over two chemotherapy cycles (i.e., prior to chemotherapy administration, approximately 1 week after chemotherapy administration, and approximately 2 weeks after chemotherapy administration). A total of 1331 patients who had complete data on both the anxiety and sleep disturbance measures were included in this analysis.

Instruments

Demographic and clinical measures—Patients completed a demographic questionnaire, Karnofsky Performance Status (KPS) scale,[25] Self-Administered Comorbidity Questionnaire (SCQ),[26] Alcohol Use Disorders Identification Test (AUDIT),[27] and a smoking history questionnaire. The toxicity of each patient's chemotherapy regimen was rated using the MAX2 score.[28] Medical records were reviewed for disease and treatment information.

Anxiety and sleep disturbance measures—The 20-items on the STAI-T and STAI-S were rated from 1 to 4.[29] 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. Cut-off scores of ≥31.8 and ≥32.2 indicate high levels of trait and state anxiety, respectively. In the current study, the Cronbach's alphas for the STAI-T and STAI-S were 0.92 and 0.96, respectively.

The 21-item GSDS was designed to assess various aspects of sleep disturbance (i.e., quality, quantity, onset latency, mid and early awakenings, sleep medications, daytime sleepiness). 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.[30-32] Subscale scores of ≥3 and a GSDS total score of ≥43 indicate a significant level of sleep disturbance that warrants clinical evaluation and management.[33] In this study, the Cronbach's alpha for the GSDS total score was 0.83.

Other symptom measures—An evaluation of other common symptoms was done using valid and reliable instruments. The symptoms and their respective measures were: depressive symptoms (Center for Epidemiological Studies-Depression scale (CES-D)[34]); morning and evening fatigue and morning and evening energy (Lee Fatigue Scale (LFS)[35]); cognitive function (Attentional Function Index (AFI)[36]); and pain (Brief Pain Inventory (BPI)[37]).

QOL measures—QOL was evaluated using generic (i.e., Medical Outcomes Study-Short Form-12 (SF-12)[38]) and disease-specific (i.e., QOL-Patient Version (QOL-PV)[39]) measures. The individual items on the SF-12 were evaluated and the instrument was scored into two component scores (i.e., physical component summary (PCS) and mental component summary (MCS)). QOL-PV measures four dimensions of QOL (i.e., physical, psychological, social, and spiritual well-being), as well as a total QOL score. For both measures, higher scores indicate a better QOL.

Data Analysis

LPA was used to identify subgroups of patients with distinct anxiety AND sleep disturbance profiles. Using Mplus version 8.4,[40] this LPA was done with the combined set of variables over time (i.e., using the STAI-S AND GSDS total scores obtained during the six assessments in a single LPA). This approach provides a profile description of these two symptoms with parallel profiles over time.

In order to incorporate expected correlations among the repeated measures of the same variable and cross-correlations of the series of the two variables (i.e., STAI-S and GSDS total scores), we included covariance parameters among measures at the same occasion and those that were one or two occasions apart. Covariances of each variable with the other at the same assessments were included in the model and autoregressive covariances were estimated with a lag of two with the same measures and with a lag of one for each variable's series with the other variable. We limited the covariance structure to a lag of two to accommodate the expected reduction in the correlations that would be introduced by two chemotherapy cycles within each set of three measurement occasions and to reduce model complexity.[41]

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 solution that best characterized the observed latent class structure with the Bayesian Information Criterion,[42] Vuong-Lo-Mendell-Rubin likelihood ratio test (VLRM), entropy, and latent class percentages that were large enough to be reliable.[43] Missing data were accommodated for with the use of the Expectation-Maximization (EM) algorithm.[44]

Data were analyzed using SPSS version 27 (IBM Corporation, Armonk, NY). Differences among the anxiety AND sleep disturbance classes in demographic, clinical, and symptom characteristics, and QOL outcomes at enrollment were evaluated using parametric and nonparametric tests. Bonferroni corrected p-value of <0.017 was considered statistically significant for the pairwise contrasts (i.e., 0.05/3 possible pairwise contrasts).

Results

Latent profile analysis

A three-class solution was selected because the BIC for that solution was lower than the BIC for the 2-class solution. In addition, the VLMR was significant for the 3-class solution, indicating that three classes fit the data better than two classes. Although the BIC was smaller for the 4-class than for the 3-class solution, the VLMR was not significant for the 4-class solution, indicating that too many classes were extracted (Table 1).

Based on clinically meaningful cutoff scores,[29, 33] as shown in Figure 1, the state anxiety AND sleep disturbance latent classes were classified as "no anxiety and low sleep disturbance" (59.7%, No ANX+Low SD); "moderate anxiety and high sleep disturbance" (32.5%, Mod ANX+High SD); and "high anxiety and very high sleep disturbance" (7.8%, High ANX+Very High SD). For the No ANX+Low SD and the Mod ANX+High SD

classes, state anxiety and sleep disturbance scores increased slightly at the second and fifth assessments (i.e., following the administration of chemotherapy). For the High ANX+Very High SD class, state anxiety and sleep disturbance scores increased at the second assessment and remained relatively stable over time.

Differences in demographic and clinical characteristics

Compared to the No ANX+Low SD class, the other two classes were significantly younger; more likely to self-report being of Hispanic or Mixed ethnicity; less likely to be married or partnered; had a lower annual household income; were more likely to report childcare responsibilities; and more likely to receive an antiemetic regimen that contained a neurokin-1 (NK-1) receptor antagonist and two other antiemetics (Table 2). Compared to the No ANX+Low SD class, the Mod ANX+High SD class was more likely to be female; more likely to live alone; less likely to be employed; more likely to report elder care responsibilities; and had a higher MAX2 score.

Compared to the No ANX+Low SD class, the High ANX+Very High SD class was less likely to exercise on a regular basis and more likely to self-report diagnoses of ulcer or stomach disease, kidney disease, and anemia or blood disease. In addition, significant differences were found among the three classes in KPS scores (i.e., No ANX+Low SD > Mod ANX+High SD > High ANX+Very High SD), as well as total number of comorbid conditions, SCQ scores, and self-reported diagnoses of depression and back pain that followed the same pattern (i.e., No ANX+Low SD < Mod ANX+High SD < High ANX+Very High SD; Table 2).

Differences in sleep disturbance subscale scores

For the sleep quality, sleep onset latency, early awakenings, excessive daytime sleepiness subscale scores as well as for the total GSDS score, significant differences among the three latent classes followed the same pattern (i.e., No ANX+Low SD < Mod ANX+High SD < High ANX+Very High SD; Table 3). Compared to the No ANX+Low SD class, patients in the other two classes reported higher scores for sleep quantity (i.e., fewer hours of sleep), mid-sleep awakenings, and use of medications for sleep.

Differences in common symptoms

As shown in Table 4, for depressive symptoms, trait and state anxiety, morning and evening fatigue, and pain interference scores, differences among the latent classes followed the same pattern (i.e., No ANX+Low SD < Mod ANX+High SD < High ANX+Very High SD). In terms of morning and evening energy and cognitive function scores, differences among the latent classes followed the same pattern (i.e., No ANX+Low SD > Mod ANX+High SD > High ANX+Very High SD). Compared to the No ANX+Low SD class, a higher percentage of patients in the other two classes reported the occurrence of both cancer and non-cancer pain and higher worst pain intensity scores.

Differences in QOL

As shown in Figure 2, for the SF-12's role physical, bodily pain, general health, vitality, social functioning, role emotional, mental health, and MCS scores, differences among the

classes followed the same pattern (i.e., No ANX+Low SD > Mod ANX+High SD > High ANX+Very High SD). For the physical functioning and PCS scores, compared to the No ANX+Low SD class, patients in the other two classes reported lower scores.

For the QOL-PV's physical well-being, psychological well-being, social well-being, and spiritual well-being subscale scores as well as for the total QOL scores, differences among the classes followed the same pattern (i.e., No ANX+Low SD > Mod ANX+High SD > High ANX+Very High SD; Figure 3).

Discussion

This study is the first to use LPA to identify subgroups of patients with distinct anxiety AND sleep disturbance profiles and to evaluate for differences in demographic, clinical, and symptom characteristics, as well as QOL outcomes among the three profiles. While our previous analyses identified four distinct classes for anxiety[15] and three for sleep disturbance,[17] when these two symptoms were modeled together, three distinct classes were identified. Of note, 40.3% of the patients reported moderate to high levels of anxiety and high to very high levels of sleep disturbance. However, all of our patients reported total sleep disturbance scores that were above the clinically meaningful cutoff (i.e., ≥43). While our occurrence rates for moderate to high levels of anxiety were similar to previous systematic reviews,[10, 11] our sleep disturbance rates are higher than the 30% to 88% reported in previous studies of patients undergoing chemotherapy.[18, 20] This inconsistent finding may be related to heterogeneity in the types of cancers that were evaluated; the timing of the assessments; and/or the instruments that were used to evaluate sleep disturbance. Additional research is needed to confirm our findings across the entire course of chemotherapy treatment using both subjective and objective measures.

A comparison of the joint trajectories for the anxiety AND sleep disturbance scores over time (i.e., Figure 1) suggests that the two symptoms fluctuate in a similar pattern (i.e., both scores increase slightly following the administration of chemotherapy). The similarities between the anxiety and sleep disturbance trajectories regardless of the severity profile, are consistent with prior reports that suggest that anxiety and sleep disturbance often evolve concurrently[14, 21, 45-47] and are moderately correlated in both oncology patients (e.g., r =0.47[46]) and individuals in the general populations (e.g., r =0.58[48]). In addition, in a study of the general population,[47] individuals who experienced sleep disturbance were 9.8 times more likely to report anxiety.

Several plausible hypotheses can explain the co-occurrence of these two symptoms. One hypothesis is that they anxiety and sleep disturbance share common underlying mechanisms.[45, 47, 49, 50] For example, increased hyperarousal, associated with dysregulation of cholinergic and gamma aminobutyric acid (GABA) systems, may be involved in the co-occurrence of anxiety and sleep disturbance.[47] In addition, emerging evidence suggests that higher levels of anxiety and sleep disturbance are associated with changes in levels of pro and anti-inflammatory cytokines.[49-51] For example, polymorphisms in the nuclear factor kappa beta 2 gene were associated with higher levels of trait anxiety[49] and sleep disturbance in oncology patients undergoing radiation therapy and their family caregivers.[50] Higher

concentrations of circulating interleukin 6 (IL-6) were associated with higher levels of anxiety[52] and sleep disturbance[51] in studies of oncology patients and the general population, respectively. In addition, in a study of healthy individuals that evaluated the relationships among abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis activity and sleep quality,[53] subtle changes in HPA responses (measured using the cortisol awakening response) and higher trait anxiety was associated with poorer sleep quality and lower cognitive function. An equally plausible explanation is that cancer and its treatments are perceived by some patients as life threatening events that contribute to persistent anxiety and sleep disturbance.[54] Additional research is needed to replicate our profiles and determine the underlying mechanisms that may contribute to higher levels of individual symptoms, as well as the joint symptom profiles.

Sleep disturbance characteristics

As shown in Table 3, all of our patients had a total GSDS score that was above the clinically meaningful cutoff (i.e., ≥43.0) across all six assessments. In terms of its clinical context, the scores for our two highest classes are comparable to those reported by permanent shift workers (i.e., 60.5)[31] and mothers of newborn infants (i.e., 55.5).[55] In addition, the total GSDS scores for these two highest classes are higher than patients undergoing radiation therapy (i.e., 44.3 (breast cancer),[56] 34.5 (prostate cancer)[56]) or cancer surgery (i.e., 48.1 (breast cancer),[57] 56.2 (lung cancer)[58]). It is possible that differences among the patients with types of cancers and/or treatments may be related to the presence of a sleep disturbance prior to study enrollment; the timing of the sleep disturbance assessments; or the use of sleep medications. In addition, it is possible that different cancer treatments may have differential effects on the magnitude of inflammatory processes and associated symptom burden.

All three latent classes reported insufficient quantity of sleep and problems with sleep maintenance (i.e., mid-sleep awakenings, early awakenings). However, patients in the two highest classes also reported poorer quality of sleep, difficulty initiating sleep (i.e., sleep onset latency) and excessive daytime sleepiness for more than 4 days per week which suggests problems with both initiation and maintenance of sleep. These findings are consistent with a review that reported that even with low levels of anxiety, sleep disturbance was a common problem in oncology patients.[59] Given that sleep disturbance tends to persist for long periods of time,[60] clinicians need to conduct routine assessments of sleep disturbance and educate patients to use appropriate sleep management interventions (e.g., scheduled bed and wake times).

Demographic and clinical characteristics

Table 5 summarizes the risk factors associated with the two highest anxiety and sleep disturbance profiles. Compared to the No ANX+Low SD class, several common risk factors were associated with membership in the other two classes, namely: younger age, more likely to self-report being of Hispanic or Mixed ethnicity, less likely to be married or partnered, more likely to have lower annual household income, and more likely to have child care responsibilities. In terms of age, while in some studies no association was found between age and anxiety[5] and age and sleep disturbance,[22] others found that younger oncology patients reported higher levels of anxiety[61] and sleep disturbance.[62] Given that younger

patients tend to develop more aggressive types of cancers that warrant more aggressive treatments,[63, 64] they may have higher levels of anxiety and sleep disturbance because of concerns about changes in their physical appearance, fertility), and survival.[61] In addition, a cancer diagnosis at a younger age can be more stressful because these patients may be trying to establish themselves professionally or be raising young children, which would have a significant impact on their physical and mental health.[65]

Several lines of evidence support our profile associations with marital status, child care responsibilities and income. For example, in one study,[66] support during chemotherapy, particularly in relationship to child care, was provided by the patient's intimate partner. The lack of adequate support at home with activities of daily living, not only places increased demands on the patient, but may contribute to a lower socioeconomic status because of loss of work productivity during the treatment.[67-69] Increased stress, lack of support, and financial hardship associated with inability to work may exacerbate anxiety and sleep disturbance.[20, 68, 70] Additional research that incorporates measures of social support, as well as other social determinants of health, is needed to confirm our findings and determine more definitive associations.

In terms of clinical characteristics, compared to the No ANX+Low SD class, membership in the other two classes was associated with a higher overall comorbidity burden, lower functional status, self-reported diagnoses of depression and back pain, and receiving an antiemetic regimen containing a neurokin-1 (NK-1) receptor antagonist in combination with other two antiemetics. Our findings are consistent with previous studies of oncology patients that found that a higher comorbidity burden and a poorer functional status increase the likelihood of anxiety[71-73] and sleep disturbance.[74] Given the bi-directional relationships between depression, anxiety, and sleep disturbance,[5, 75] it is not surprising that patients with higher levels of anxiety and sleep disturbance self-reported a diagnosis of depression, because several factors (e.g., genetic, social, environmental)[75-77] and common inflammatory and neurobiological pathways[75] may be involved in the development of all three symptoms during chemotherapy. In addition, while not evaluated in patients undergoing chemotherapy specifically, back pain was found to be prevalent in oncology patients and was associated with anxiety and sleep disturbance experienced during various cancer treatments (e.g., chemotherapy, surgery).[78] Since higher comorbidity burden and lower functional status are associated with higher levels of anxiety and sleep disturbance during chemotherapy, clinicians need to remain vigilant and conduct routine assessments, particularly in patients with higher number of comorbidities.

Common symptoms

In terms of the differences in the severity of common symptoms, significant differences were found among the latent classes, in a stepwise fashion, in depressive symptoms, trait and state anxiety, morning and evening fatigue, as well as decrements in morning and evening energy and cognitive function, suggesting additive or synergistic effects (Table 4). Of note, while all three classes had morning energy scores below the clinically meaningful cutoff score (i.e., ≤6.2), for the two higher symptom profiles, all of the other symptom scores were above the clinically meaningful cutoff. Emerging evidence suggests

that some of these symptoms occur in clusters during chemotherapy[7] because they may share common biological mechanisms.[79, 80] Additional research is warranted to evaluate the causal relationships among the most common symptoms associated with cancer and its treatments and the co-occurrence of anxiety AND sleep disturbance.

Consistent with prior reports that found that patients with higher levels of pain were more likely to experience anxiety[81, 82] and sleep disturbance,[83] compared with the 22.9% of patients No ANX+Low SD class, 39.6% and 50.5% of the patients in the Mod ANX+High SD and High ANX+Very High SD classes, respectively, reported both cancer and non-cancer pain. In addition, the patients in these highest two classes had moderate to severe pain and pain interference. These findings are not surprising given that pain is one of the most prevalent and burdensome symptoms reported by oncology patients[84, 85] and is often undertreated.[83, 86] For example, in one study,[86] uncontrolled cancer pain was found to be a risk factor for higher levels of state anxiety. In another study that examined the relationship between anxiety and pain,[81] patients with pain were 4.44 more likely to report anxiety than patients without pain. A similar pattern is noted for sleep disturbance. In a study that evaluated factors that affect sleep in cancer patients,[87] undertreatment of pain was found to be an important risk factor of poor sleep quality, daytime tiredness, and problems with initiation and maintenance of sleep. Given that information on the specific causes of pain were not obtained in this study, additional research is warranted on the effects of acute and chronic pain on the co-occurrence of anxiety and sleep disturbance.

QOL outcomes

Consistent with prior studies that reported associations between anxiety and sleep disturbance as single symptoms decrements in QOL in both oncology patients[88, 89] and general populations,[90, 91] for all of the general and disease-specific QOL domains, as the anxiety and sleep disturbance profiles worsened, all aspects of QOL were impacted. Of note, for both the PCS and MCS scores, patients with the two worst profiles, reported scores of less than 50, which is lower than the normative score for the general population.[39] Furthermore, compared with the No ANX+Low SD class, all of the differences across the various domains of QOL in the High ANX+Very High SD class represent not only statistically significant but clinically meaningful differences ($d = 0.52–2.74$). Our findings can be partially explained by the fact that patients undergoing chemotherapy often experience multiple co-occurring symptoms that affect all aspects of their daily life.

Limitations

Some limitations need to be acknowledged. First, anxiety and sleep disturbance were measured over only two cycles of chemotherapy. Future studies need to evaluate for changes in these two symptoms from prior to through the completion of chemotherapy. Because our sample was relatively homogenous (e.g., White, female, educated), our findings may not be representative of all oncology patients. Third, we did not collect information on medications used to treat anxiety and sleep disturbance, which may have changed the interpretation of our findings. In addition, patients were not evaluated for specific anxiety or sleep (e.g., obstructive sleep apnea) disorders. Lastly, the major reason for refusal to participate in the

study was being overwhelmed with cancer treatments, which suggests that anxiety and/or sleep disturbance were under-estimated in this sample.

Conclusions and Implications for Practice

This study is the first to identify latent classes of oncology patients with distinct joint anxiety AND sleep disturbance profiles. Future research should focus on common and distinct mechanisms that may be responsible for the co-occurrence of these two symptoms. In addition, since evidence on the associations between anxiety and sleep disturbance and other common symptoms remains limited, additional research is warranted to determine the potential mechanisms that contribute to a higher multi-symptom burden. Our findings strongly suggest that patients undergoing chemotherapy experience clinically meaningful levels of both anxiety AND sleep disturbance during chemotherapy. These patients warrant referrals to psychological or other services offered by their health care system to reduce the severity of both symptoms.

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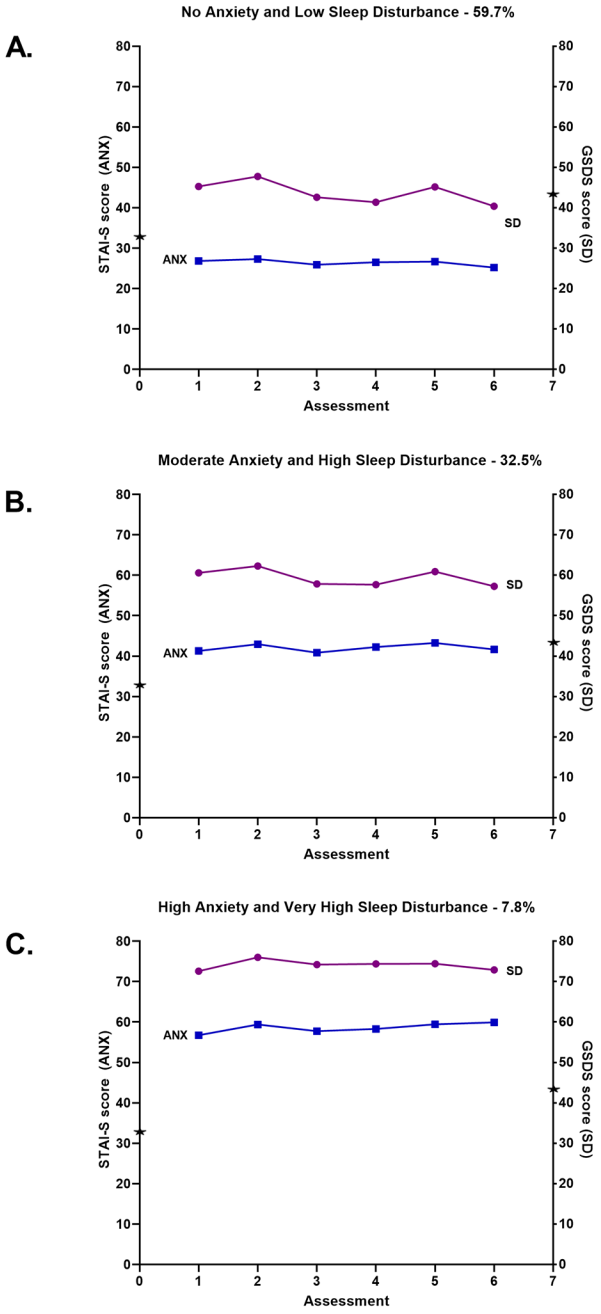

Figure 1.

Changes in Spielberger State Anxiety Inventory (STAI-S (ANX), left y-axis) and General Sleep Disturbance Scale (GSDS (SD), right y-axis) scores over two cycles of chemotherapy for subgroups of patients with No Anxiety and Low Sleep Disturbance (panel A), Moderate Anxiety and High Sleep Disturbance (panel B), and High Anxiety and Very High Sleep D (panel C).

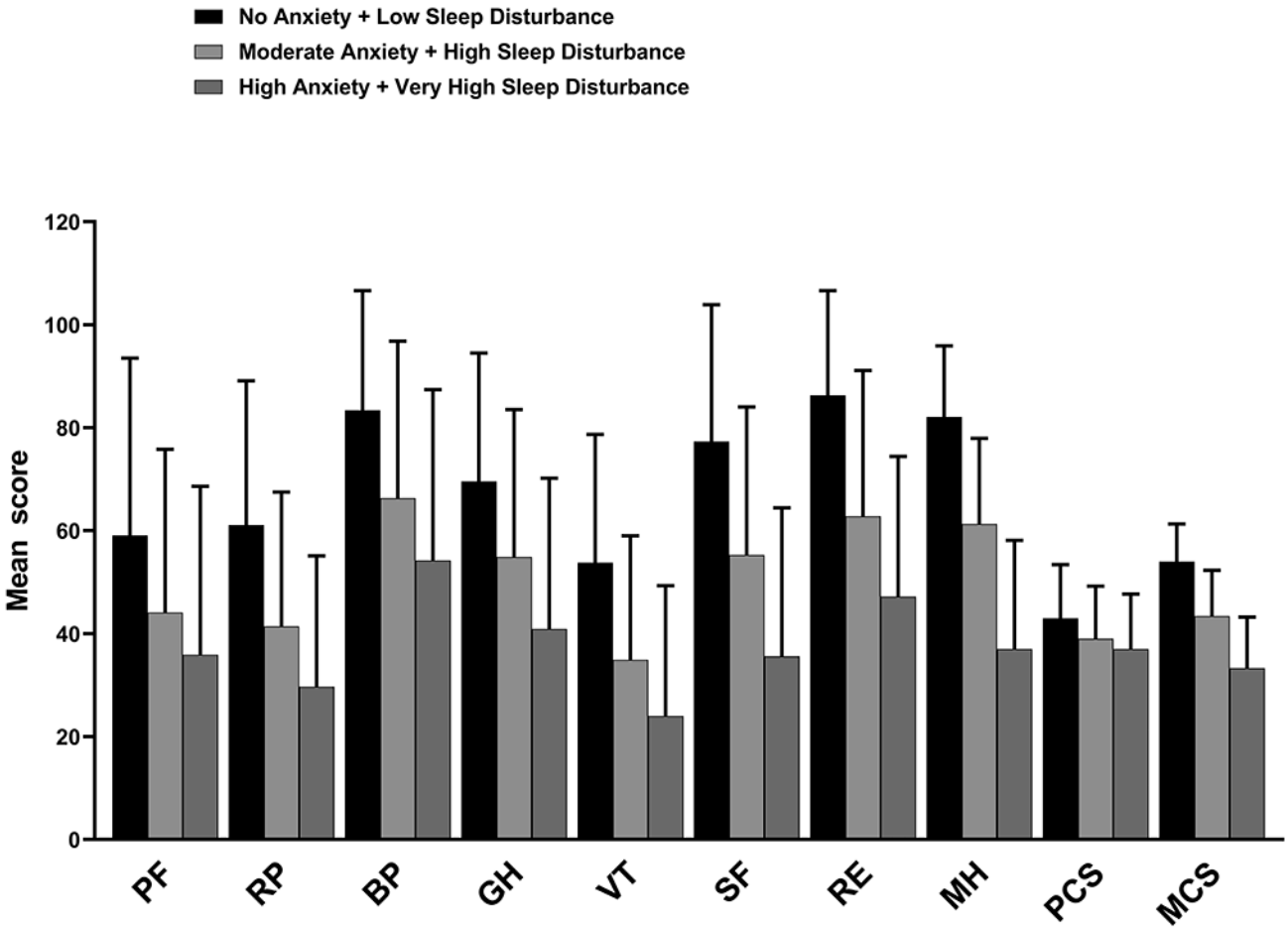

Figure 2.

Differences in Medical Outcomes Study - Short Form-12 physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), mental health (ME), physical component summary (PCS), and mental component summary (MCS) scores among the anxiety and sleep disturbance latent classes. All values are plotted as means ± standard deviations. For the RP, BP, GH, VT, SF, RE, MH, and MCS domains, post hoc contrasts demonstrated that the differences among the classes followed the same pattern (i.e., No Anxiety and Low Sleep Disturbance class > Moderate Anxiety and High Sleep Disturbance class > High Anxiety and Very High Sleep Disturbance class (all, $p < 0.00$)). For the PF and PCS domains, post hoc contrasts demonstrated that that the differences among the classes were as follows: No anxiety and Low Sleep Disturbance class > Moderate Anxiety and High Sleep Disturbance and High Anxiety and Very High Sleep Disturbance classes (both, $p < 0.001$).

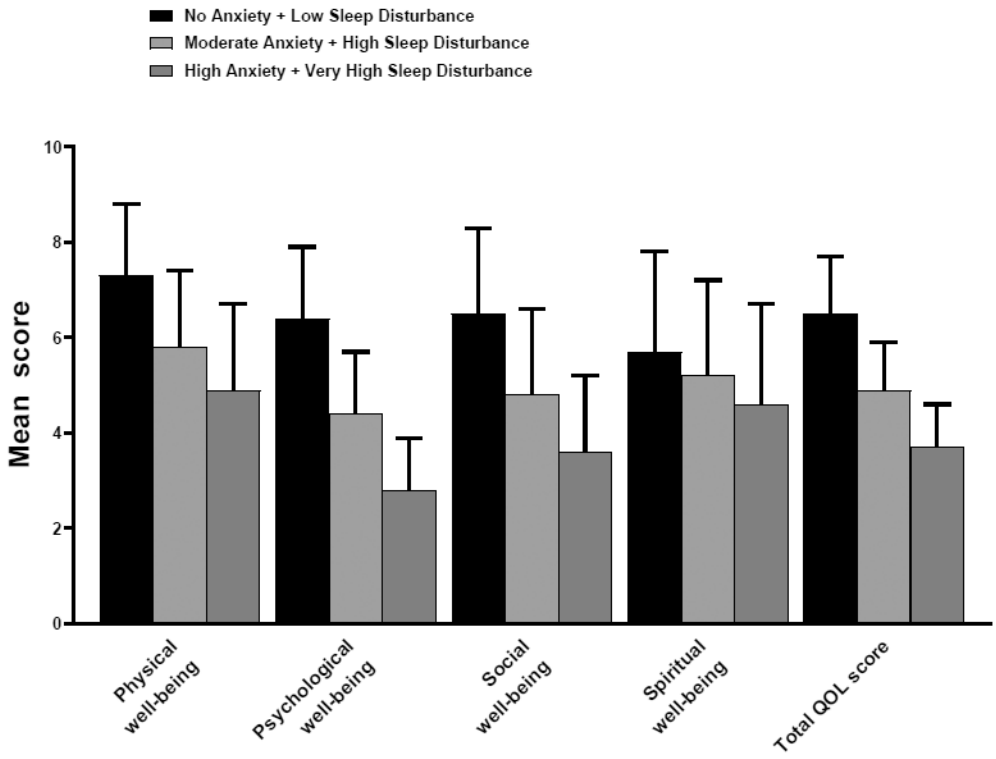

Figure 3.

Differences in mean Quality of Life Scale – Patient Version physical, psychological, social, and spiritual well-being domains as well as total quality of life (QOL) scores among the anxiety and sleep disturbance latent classes. All values are plotted as means ± standard deviations. For all of the subscales as well as the total scores, post hoc contrasts demonstrated that significant differences among the classes followed the same pattern (i.e., No Anxiety and Low Sleep Disturbance class > Moderate Anxiety and High Sleep Disturbance class > High Anxiety and Very High Sleep Disturbance class (all, $p < 0.001$)).

Table 1.

Latent Profile Solutions and Fit Indices for One through Four Classes for Spielberger State Anxiety and General Sleep Disturbance Scores

Model	LL	AIC	BIC	Entropy	VLMR
1 Class	−52832.90	105781.79	106083.02	n/a	n/a
2 Class	−51978.54	104099.09	104467.84	0.85	1708.70 [c]
3 Class[a]	−51688.00	103544.01	103980.28	0.87	581.08 [b]
4 Class	−51434.17	103062.34	103566.13	0.81	ns

Baseline entropy and VLMR are not applicable for the one-class solution

[a]The 3-class solution was selected because the BIC for that solution was lower than the BIC for the 2-class solution. In addition, the VLMR was significant for the 3-class solution, indicating that three classes fit the data better than two classes. Although the BIC was smaller for the 4-class than for the 3-class solution, the VLMR was not significant for the 4-class solution, indicating that too many classes were extracted.

[b]$p < .005$

[c]$p < .00005$

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; LL, log-likelihood; n/a, not applicable; ns, not significant; 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 Combined State Anxiety and Sleep Disturbance Latent Classes

Characteristic	No Anxiety + Low Sleep Disturbance (0) 59.7% (n=794)	Moderate Anxiety + High Sleep Disturbance (1) 32.5% (n=433)	High Anxiety + Very High Sleep Disturbance (2) 7.8% (n=104)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	58.7 (11.9)	55.1 (12.9)	54.2 (11.7)	F=15.51, p<.001 0 > 1 and 2
Education (years)	16.3 (3.0)	16.1 (3.0)	15.9 (3.1)	F=1.26, p=.284
Body mass index (kg/m^2)	25.9 (5.3)	26.5 (6.2)	26.7 (6.1)	F=1.61, p=.200
Alcohol Use Disorders Identification Test score	2.9 (2.2)	3.1 (2.8)	2.9 (3.1)	F=0.68, p=.505
Karnofsky Performance Status score	83.1 (11.8)	76.3 (12.1)	70.9 (11.3)	F=75.70, p<.001 0 > 1 > 2
Number of comorbid conditions	2.2 (1.3)	2.6 (1.5)	3.2 (1.6)	F=27.14, p<.001 0 < 1 < 2
Self-administered Comorbidity Questionnaire score	4.9 (2.9)	6.0 (3.4)	7.6 (3.8)	F=41.72, p<.001 0 < 1 < 2
Time since diagnosis (years)	2.0 (3.8)	2.2 (4.4)	1.1 (2.0)	KW=3.39, p=.184
Time since diagnosis (years, median)	0.42	0.42	0.42	
Number of prior cancer treatments	1.6 (1.5)	1.7 (1.5)	1.5 (1.4)	F=0.77, p=.462
Number of metastatic sites including lymph node involvement[a]	1.3 (1.2)	1.2 (1.3)	1.2 (1.2)	F=0.19, p=.828
Number of metastatic sites excluding lymph node involvement	0.8 (1.0)	0.8 (1.1)	0.7 (1.0)	F=0.63, p=.533
MAX2 score	0.17 (0.08)	0.18 (0.08)	0.18 (0.09)	F=3.48, p=.031 0 <1
	% (n)	% (n)	% (n)	
Gender (% female)	74.7 (592)	83.4 (361)	80.4 (84)	X^2=12.91, p=.002 0 < 1
Self-reported ethnicity White Asian or Pacific Islander Black Hispanic, Mixed, or Other	71.4 (559) 12.9 (101) 7.7 (60) 8.0 (63)	67.9 (290) 11.9 (51) 6.1 (26) 14.1 (18)	62.5 (65) 11.5 (12) 8.7 (9) 17.3 (18)	X^2=16.68, p=.011 NS NS NS 0 < 1 and 2
Married or partnered (% yes)	68.8 (539)	59.8 (254)	51.0 (53)	X^2=18.92, p<.001 0 > 1 and 2
Lives alone (% yes)	18.5 (145)	26.0 (111)	26.0 (27)	X^2=10.37, p=.006 0 < 1
Currently employed (% yes)	39.7 (311)	27.5 (118)	30.8 (32)	X^2=18.92, p<.001 0 > 1

Characteristic	No Anxiety + Low Sleep Disturbance (0) 59.7% (n=794)	Moderate Anxiety + High Sleep Disturbance (1) 32.5% (n=433)	High Anxiety + Very High Sleep Disturbance (2) 7.8% (n=104)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Annual household income Less than $30,000 $30,000 to $70,000 $70,000 to $100,000 Greater than $100,000	13.1 (92) 21.0 (147) 18.3 (128) 47.6 (333)	22.7 (90) 22.5 (89) 16.2 (64) 38.6 (153)	40.0 (38) 16.8 (16) 9.5 (9) 33.7 (32)	KW=30.38, p<.001 0 > 1 and 2
Childcare responsibilities (% yes)	19.2 (149)	25.4 (107)	31.7 (33)	X^2=12.10, p=.002 0 < 1 and 2
Elder care responsibilities (% yes)	6.5 (47)	11.0 (43)	6.1 (6)	X^2=7.37, p=.025 0 < 1
Past or current history of smoking (% yes)	34.0 (266)	35.5 (151)	44.1 (45)	X^2=4.05, p=.132
Exercise on a regular basis (% yes)	73.3 (573)	68.5 (287)	61.0 (61)	X^2=8.03, p=.018 0 > 2
Specific comorbid conditions				
Heart disease	5.7 (45)	6.7 (29)	1.9 (2)	X^2=3.56, p=.169
High blood pressure	30.9 (245)	27.5 (119)	36.5 (38)	X^2=3.66, p=.160
Lung disease	10.7 (85)	11.3 (49)	16.3 (17)	X^2=2.91, p=.233
Diabetes	8.4 (67)	8.8 (38)	13.5 (14)	X^2=2.87, p=.238
Ulcer or stomach disease	3.8 (30)	5.3 (23)	11.5 (12)	X^2=12.18, p=.002 0 < 2
Kidney disease	0.9 (7)	1.8 (8)	3.8 (4)	X^2=6.55, p=.038 0 < 2
Liver disease	6.9 (55)	6.5 (28)	2.9 (3)	X^2=2.49, p=.288
Anemia or blood disease	10.5 (83)	13.6 (59)	21.2 (22)	X^2=10.76, p=.005 0 < 2
Depression	9.6 (76)	29.3 (127)	51.9 (54)	X^2=147.23, p<.001 0 < 1 < 2
Osteoarthritis	11.7 (93)	13.2 (57)	10.6 (11)	X^2=0.80, p=.670
Back pain	19.6 (156)	31.6 (137)	47.1 (49)	X^2=48.22, p<.001 0 < 1 < 2
Rheumatoid arthritis	3.1 (25)	3.0 (13)	3.8 (4)	X^2=0.20, p=.907
Cancer diagnosis Breast cancer Gastrointestinal cancer	39.3 (312) 31.9 (253) 17.3 (137) 11.6 (92)	41.6 (180) 28.4 (123) 18.7 (81) 11.3 (49)	43.3 (45) 27.9 (29) 13.5 (14) 15.4 (16)	X^2=4.55, p=.603

Characteristic	No Anxiety + Low Sleep Disturbance (0) 59.7% (n=794)	Moderate Anxiety + High Sleep Disturbance (1) 32.5% (n=433)	High Anxiety + Very High Sleep Disturbance (2) 7.8% (n=104)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Gynecological cancer Lung cancer				
Prior cancer treatment No prior treatment Only surgery, CTX, or RT Surgery and CTX, or surgery and RT, or CTX and RT Surgery and CTX and RT	26.2 (202) 40.7 (314) 21.6 (167) 11.5 (89)	22.7 (96) 43.8 (185) 17.5 (74) 15.9 (67)	26.2 (27) 43.7 (45) 15.5 (16) 14.6 (15)	X^2=9.48, p=.148
Metastatic sites No metastasis Only lymph node metastasis Only metastatic disease in other sites Metastatic disease in lymph nodes and other sites	31.8 (250) 21.1 (166) 22.7 (179) 24.4 (192)	33.4 (142) 22.4 (95) 19.1 (81) 25.2 (107)	34.0 (35) 26.2 (27) 17.5 (18) 22.3 (23)	X^2=4.22, p=.647
Receipt of targeted therapy No Yes	68.3 (533) 31.7 (247)	72.0 (304) 28.0 (118)	73.5 (75) 26.5 (27)	X^2=2.47, p=.291
Cycle length 14-day cycle 21-day cycle 28-day cycle	43.3 (342) 49.0 (387) 7.7 (61)	39.8 (170) 53.6 (229) 6.6 (28)	39.2 (40) 53.9 (55) 6.9 (7)	KW=0.88, p=.644
Emetogenicity of the CTX regimen Minimal/low Moderate High	19.2 (152) 62.7 (495) 18.1 (143)	19.9 (85) 58.2 (249) 22.0 (94)	20.6 (21) 60.8 (62) 18.6 (19)	KW=0.84, p=.657
Antiemetic regimen None Steroid alone or serotonin receptor antagonist alone Serotonin receptor antagonist and steroid NK-1 receptor antagonist and two other antiemetics	8.1 (63) 20.7 (161) 49.6 (385) 21.5 (167)	5.8 (24) 20.9 (86) 45.4 (187) 27.9 (115)	5.0 (5) 17.8 (18) 42.6 (43) 34.7 (35)	X^2=13.71, p=.033 NS NS NS 0 < 1 and 2

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

Abbreviations: CTX, chemotherapy; kg, kilograms; KW, Kruskal Wallis; m^2, meters squared; n/a, not applicable; NK-1, neurokinin-1; NS, not significant; pw, pairwise; SD, standard deviation; RT, radiation therapy.

Table 3.

Differences Subscale Scores for the General Sleep Disturbance Scale at Enrollment

Subscales for the General Sleep Disturbance Scale [a]	No Anxiety + Low Sleep Disturbance (0) 59.7% (n=794)	Moderate Anxiety + High Sleep Disturbance (1) 32.5% (n=433)	High Anxiety + Very High Sleep Disturbance (2) 7.8% (n=104)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Quality of sleep (≥3)	2.8 (1.7)	3.9 (1.6)	4.8 (1.6)	F=104.72, p<.001 0 < 1 < 2
Quantity of sleep (≥3)	4.5 (1.5)	4.7 (1.6)	5.0 (1.9)	F=6.87, p=.001 0 < 1 and 2
Sleep onset latency (≥3)	2.2 (2.1)	3.2 (2.2)	4.4 (2.3)	F=60.06, p<.001 0 < 1 < 2
Mid-sleep awakenings (≥3)	4.7 (2.3)	5.1 (2.0)	5.5 (1.9)	F=8.13, p<.001 0 < 1 and 2
Early awakenings (≥3)	3.1 (2.5)	4.1 (2.3)	5.2 (2.0)	F=50.45, p<.001 0 < 1 < 2
Medications for sleep (≥3)	0.5 (0.7)	0.8 (0.8)	0.9 (0.9)	F=28.54, p<.001 0 < 1 and 2
Excessive daytime sleepiness (≥3)	2.1 (1.3)	3.3 (1.3)	4.0 (1.4)	F=173.30, p<.001 0 < 1 < 2
Total GSDS Score (≥43)	45.1 (18.3)	61.2 (17.2)	72.9 (17.5)	F=180.40, p<.001 0 < 1 < 2

Abbreviations: GSDS, General Sleep Disturbance Scale; SD, standard deviation.

[a]Numbers in parentheses indicate clinically meaningful cutoff scores

Table 4.

Differences in Common Symptom Severity Scores Among the Combined State Anxiety and Sleep Disturbance Latent Classes

Symptoms[a]	No Anxiety + Low Sleep Disturbance (0) 59.7% (n=794)	Moderate Anxiety + High Sleep Disturbance (1) 32.5% (n=433)	High Anxiety + Very High Sleep Disturbance (2) 7.8% (n=104)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Depressive symptoms (≥16.0)	7.9 (5.8)	17.9 (7.9)	29.8 (10.6)	F=601.61, p<.001 0 < 1 < 2
Trait anxiety (≥31.8)	29.2 (6.0)	41.8 (8.2)	53.1 (8.9)	F=781.70, p<.001 0 < 1 < 2
State anxiety (≥32.2)	26.8 (6.5)	41.5 (9.1)	57.2 (11.2)	F=954.87, p<.001 0 < 1 < 2
Morning fatigue (≥3.2)	2.3 (1.9)	4.1 (2.2)	5.2 (2.2)	F=163.61, p<.001 0 < 1 < 2
Evening fatigue (≥5.6)	4.9 (2.1)	5.9 (1.9)	6.7 (1.8)	F=55.79, p<.001 0 < 1 < 2
Morning energy (≤6.2)	4.8 (2.3)	4.0 (2.0)	3.4 (2.2)	F=29.15, p<.001 0 > 1 > 2
Evening energy (≤3.5)	3.8 (2.1)	3.3 (1.9)	2.8 (2.2)	F=13.84, p<.001 0 > 1 > 2
Attentional function (<5.0 = Low, 5 to 7.5 = Moderate, >7.5 = High)	7.1 (1.5)	5.5 (1.6)	4.7 (1.8)	F=207.67. p<.001 0 > 1 > 2
Types of pain None Only non-cancer pain Only cancer pain Both non-cancer and cancer pain	 33.9 (265) 17.5 (137) 25.6 (200) 22.9 (179)	 19.9 (84) 13.3 (56) 27.3 (115) 39.6 (167)	 8.7 (9) 13.6 (14) 27.2 (28) 50.5 (52)	X^2=77.34, p<.001 0 > 1 > 2 NS NS 0 < 1 and 2
For the patients with pain	Mean (SD)	Mean (SD)	Mean (SD)	
Worst pain intensity score	5.6 (2.5)	6.6 (2.5)	7.0 (2.4)	F=21.43, p<.001 0 < 1 and 2
Mean pain interference score	2.3 (2.0)	3.8 (2.6)	5.0 (2.8)	F=77.68, p<.001 0 < 1 < 2

Abbreviation: SD, standard deviation.

[a]Clinically meaningful cutoff scores

Table 5.

Characteristics Associated with Membership in the Other Two Anxiety and Sleep Disturbance Latent Classes Compared to the No Anxiety and Low Sleep Disturbance Class

Characteristic	Moderate Anxiety + High Sleep Disturbance	High Anxiety + Very High Sleep Disturbance
Demographic Characteristics		
More likely to be younger	■	■
More likely to be female	■	
Less likely to be married or partnered	■	■
More likely to live alone	■	
Less likely to be employed	■	
More likely to have a lower annual household income	■	■
Less likely to exercise on a regular basis		■
More likely to self-report as Hispanic, Mixed, or Other	■	■
More likely to have childcare responsibilities	■	■
More likely to have elder care responsibilities	■	
Clinical Characteristics		
Lower functional status (KPS score)	■	■
Higher chemotherapy toxicity (MAX2 score)	■	
Higher number of comorbidities	■	■
Higher comorbidity burden (SCQ score)	■	■
More likely to self-report anemia or blood disease		■
More likely to self-report depression	■	■
More likely to self-report back pain	■	■
More likely to self-report ulcer or stomach disease		■
More likely to self-report kidney disease		■
More likely to receive an NK-1 receptor antagonist and two other antiemetics	■	■
Sleep Disturbance Characteristics		
Lower quality of sleep	■	■
Lower quantity of sleep	■	■
Worse sleep onset latency	■	■
Higher level of mid-sleep awakenings	■	■
Higher level of early awakenings	■	■
Higher use of medications for sleep	■	■
Higher level of excessive daytime sleepiness	■	■
Higher level of overall sleep disturbance	■	■
Symptom Characteristics		
Higher depressive symptoms	■	■
Higher trait anxiety	■	■

Characteristic	Moderate Anxiety + High Sleep Disturbance	High Anxiety + Very High Sleep Disturbance
Higher state anxiety	■	■
Higher morning fatigue	■	■
Higher evening fatigue	■	■
Lower morning energy	■	■
Lower evening energy	■	■
Lower cognitive function	■	■
More likely to report both cancer and non-cancer pain	■	■
Higher worst pain intensity	■	■
Higher pain interference	■	■
Quality of Life Outcomes		
Medical Outcomes Study – Short Form 12		
Lower physical functioning	■	■
Lower role physical	■	■
Lower bodily pain	■	■
Lower general health	■	■
Lower vitality	■	■
Lower social functioning	■	■
Lower role emotional	■	■
Lower mental health	■	■
Lower physical component summary score	■	■
Lower mental component summary score	■	■
Multidimensional Quality of Life Scale Cancer – Patient Version		
Lower physical well-being	■	■
Lower psychological well-being	■	■
Lower social well-being	■	■
Lower spiritual well-being	■	■
Lower total quality of life score	■	■

Abbreviations: KPS, Karnofsky Performance Status; NK-1, neurokinin 1; SCQ, Self-administered Comorbidity Questionnaire.