



ORIGINAL ARTICLE

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

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Abstract

Study Objectives: Purposes of this study 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 cycles. Self-reported 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%]) across the six assessments. Approximately 75% of the patients had a mean total GSDS score that was above the clinically meaningful cutoff score of at least 43 across all six assessments. Compared to 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.

Statement of Significance

Longitudinal studies of interindividual variability in sleep disturbance in oncology patients receiving chemotherapy are extremely limited. This study is the first to identify three subgroups of patients with distinct sleep disturbance profiles. Equally important, patients in the two subgroups with the highest levels of sleep disturbance subgroups had clinically meaningful differences in five common co-occurring symptoms (i.e. anxiety, depression, fatigue, attentional function, and pain). Clinicians who care for oncology patients need to assess for sleep disturbance and common co-occurring symptoms during the entire course of chemotherapy.

Key words: sleep disturbance; chemotherapy; cancer; latent profile analysis; anxiety; fatigue; depression; attentional function; pain

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Introduction

Sleep disturbance is a pervasive symptom that affects 30%–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].

Although 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 10 cross-sectional and 9 longitudinal studies on sleep disturbance in women with breast cancer receiving CTX [13], findings on sleep disturbance were inconsistent. Although 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 earlier [14], sleep disturbance was assessed in patients with breast cancer at three time points during CTX (i.e. before, after cycle 4, and at 1-year post-CTX). Sleep disturbance was measured using actigraphy and the Pittsburgh Sleep Quality Index (PSQI). When patients with breast cancer were compared to healthy cancer-free women, patients with breast cancer 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 1-year post-CTX. In another longitudinal study of patients with breast cancer [15], sleep disturbance was assessed using the PSQI at three time points (i.e. 3–14 days before starting CTX, day 1 of cycle 4, and 6 months after initiation of CTX). Although 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 patients with breast cancer, and assessed sleep disturbance at a limited number of time points.

In the studies cited earlier, 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, a total of 25 symptoms were reported by over 40% of the patients receiving CTX [19]. The 5 most common co-occurring symptoms 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.

Although 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 at least 18 years of age; had a diagnosis of breast, gastrointestinal (GI), gynecological, or lung cancer; had received CTX within the preceding 4 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 2234 patients were approached and 1343 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, childcare and eldercare 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 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. Subscale scores of at least 3 and a GSDS total score of at least 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 α 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 more than 31.8 and more than 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 this 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, 5.0–7.5 moderate function, >7.5 high function) [35]. The AFI has well-established reliability and validity [34]. In this study, the Cronbach's α for the total AFI score 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 at least 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 this study, the Cronbach's α 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 0–10 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 before going to bed (i.e. evening fatigue, evening energy). The LFS has established cutoff 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 this 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 before 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. before 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, version 23 (International Business Machines, Armonk, NY). Differences among the latent classes were evaluated using analyses of variance or chi-square analyses. The Bonferroni procedure was used to calculate the post hoc contrasts. A p -value of less than .05 was considered statistically significant.

LPA of sleep disturbance

As previously described for other symptoms [43, 44], 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 pretreatment assessment, an immediate posttreatment assessment, and a second posttreatment assessment were conducted 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 " \wedge ". 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. 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 nonnormality and nonindependence 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) [45, 46]. Missing data were accommodated with the use of the Expectation-Maximization algorithm [47].

Mixture models, such as LPA, are known to produce solutions at local maxima. Therefore, our models were fit with from 1000 to 2400 random starts. This approach ensured that the estimated model was replicated many times and was not due to a local maximum. Estimation was carried out with Mplus, version 7.2 [45].

Results

Characteristics of the sample

The demographic and clinical characteristics of the sample are summarized in Table 1. Of the 1331 patients, the majority were White (69.5%), married or partnered (64.5%) with a mean age of 57.1 (± 12.3) years. More than 40% of the patients were diagnosed with breast cancer and 30.4% were diagnosed with GI cancer.

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 2). In addition, the three-class solution fits 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 at least 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 3). 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.

Table 1. Demographic and clinical characteristics of the sample ($n = 1331$)

Characteristic	Mean (SD)
Age (years)	57.1 (12.3)
Education (years)	16.2 (3.0)
Body mass index (kg/m ²)	26.2 (5.6)
Karnofsky Performance Status score	80.0 (12.5)
Self-administered Comorbidity Questionnaire score	5.5 (3.2)
Time since diagnosis (years)	2.0 (3.9)
Time since diagnosis (median; years)	0.42
Number of prior cancer treatments	1.6 (1.5)
Number of metastatic sites including lymph node involvement ^a	1.2 (1.2)
Number of metastatic sites excluding lymph node involvement	0.8 (1.1)
Hemoglobin	11.5 (1.4)
Hematocrit	34.6 (4.1)
Gender (% female)	77.9 (1037)
Self-reported ethnicity	
White	69.6 (914)
Asian or Pacific Islander	12.5 (164)
Black	7.2 (95)
Hispanic, mixed, or other	10.7 (141)
Married or partnered (% yes)	64.5 (846)
Lives alone (% yes)	21.6 (283)
Currently employed (% yes)	35.0 (461)
Annual household income	
Less than \$30 000	18.5 (220)
\$30 000–\$70 000	21.2 (252)
\$70 000–\$100 000	16.9 (201)
Greater than \$100 000	43.5 (518)
Childcare responsibilities (% yes)	22.2 (289)
Eldercare responsibilities (% yes)	7.9 (96)
Exercise on a regular basis (% yes)	70.8 (921)
Cancer diagnosis	
Breast cancer	40.3 (537)
Gastrointestinal cancer	30.4 (405)
Gynecological cancer	17.4 (232)
Lung cancer	11.8 (157)
Prior cancer treatment	
No prior treatment	25.1 (325)
Only surgery, CTX, or RT	41.9 (544)
Surgery and CTX, or surgery and RT, or CTX and RT	19.8 (257)
Surgery and CTX and RT	13.2 (171)
Metastatic sites	
No metastasis	32.5 (427)
Only lymph node metastasis	21.9 (288)
Only metastatic disease in other sites	21.1 (278)
Metastatic disease in lymph nodes and other sites	24.5 (322)
Cycle length	
14-day cycle	41.8 (555)
21-day cycle	51.0 (677)
28-day cycle	7.2 (96)

CTX = chemotherapy, kg = kilograms, m² = meters squared, NS = not significant, RT = radiation therapy, SD = standard deviation.

^aTotal number of metastatic sites evaluated was nine.

Differences in GSDS subscale scores among the sleep disturbance classes

As shown in Table 4, differences were found among the sleep disturbance classes for all of the GSDS subscale scores and total sleep disturbance score at enrollment (all $ps < .001$). For all of the subscales of the GSDS (i.e. sleep quality, sleep quantity, sleep onset latency, mid-sleep awakenings, early awakenings,

Table 2. General sleep disturbance latent profile solutions and fit indices for one- through four-class solutions

Model	LL	AIC	BIC	Entropy	VLMR
1 Class	-28 080.06	56 208.12	56 332.77	n/a	n/a
2 Class	-27 692.33	55 458.66	55 650.83	.70	775.46 ^{****}
3 Class ^a	-27 447.03	54 994.05	55 253.74	.73	490.61 ^{****}
4 Class	-27 323.81	54 773.63	55 100.83	.68	46.43 [*]

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.

^aBaseline LL, not applicable for one class; * $p < .05$; **** $p < .0001$.

^bThe 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.

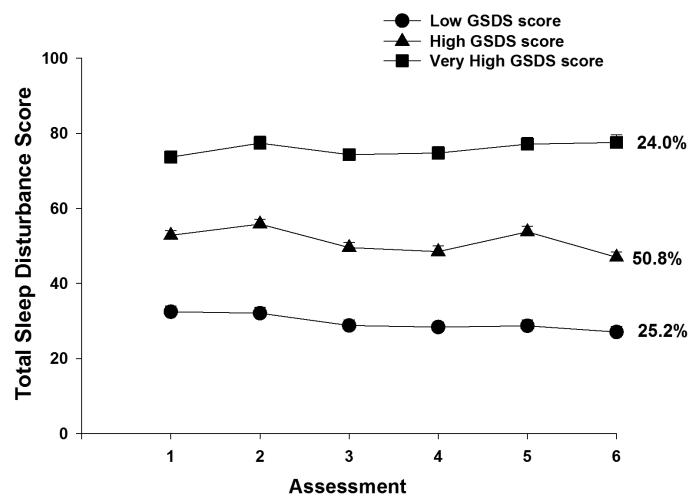


Figure 1. Sleep disturbance trajectories for patients in each of the latent classes.

medications for sleep, and excessive daytime sleepiness scores [all $ps < .001$]), 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 5](#), differences were found among the sleep disturbance classes in the severity scores for all of the co-occurring symptoms at enrollment (all $ps < .001$). 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 noncancer pain (i.e. Low < High < Very High) were in the expected directions.

Discussion

To the best of 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 at least 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%–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] [48]) and before breast cancer surgery (i.e. 48.1 [49]). 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 [50]) and permanent night shift workers (i.e. 60.5 [29]). Although the global GSDS scores among our latent classes were significantly different ([Table 4](#)), 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 [51]). Taken together, these findings suggest that a significant number of patients receiving CTX have very high levels of sleep disturbance for more than 6–8 weeks.

As shown in [Table 4](#), 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,

Table 3. 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
Gender (% female)	66.0 (221)	81.8 (553)	82.4 (263)	X ² = 37.59, p < .001 1 < 2 and 3 X ² = 8.90, p = .179
Self-reported ethnicity				
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 KW = 14.15, p < .001 1 and 2 > 3
Annual household income				
Less than \$30 000	13.6 (39)	15.2 (93)	30.0 (88)	
\$30 000-\$70 000	22.3 (64)	22.6 (138)	17.1 (50)	
\$70 000-\$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				X ² = 7.59, p = .270
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)	
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				X ² = 9.65, p = .140
No metastasis	27.3 (91)	33.3 (223)	36.1 (113)	
Only lymph node metastasis	20.4 (68)	22.9 (153)	21.4 (67)	
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				X ² = 4.12, p = .390
14-day cycle	45.2 (152)	39.5 (267)	43.0 (136)	
21-day cycle	47.3 (159)	52.8 (357)	50.9 (161)	
28-day cycle	7.4 (25)	7.7 (52)	6.0 (19)	

CTX = chemotherapy, GSDS = General Sleep Disturbance Scale, kg = kilograms, KW = Kruskal Wallis, m² = meters squared, NS = not significant, RT = radiation therapy, SD = standard deviation.

^aTotal number of metastatic sites evaluated was nine.

Table 4 – 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

GSDS = General Sleep Disturbance Scale, SD = standard deviation.

Table 5 – 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 noncancer 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 noncancer pain	18.4 (61)	27.9 (184)	48.6 (153)	1 < 2 < 3

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

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

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 of the week). Consistent with previous studies [48, 49, 51], for all three classes, the use of sleep medications was low. On the basis of 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 [51–53]. In contrast, although some studies found no gender differences [54, 55], others found that female patients reported more sleep disturbance [56–59]. 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 that the receipt of CTX resulted in a chemically induced menopause that influenced the female patients’ sleep–wake activity [60].

Although 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 heterogeneous cancer diagnoses. For example, poorer functional status [10, 28, 49, 51, 61–64] and worse comorbidity profiles [49, 51] were associated with higher levels of sleep disturbance. Consistent with a previous study of patients who underwent breast cancer surgery [49], patients with a higher BMI had worse levels of sleep disturbance. Although 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 [65–67].

Furthermore, a relationship exists between a higher BMI and lack of regular exercise [68], 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 [69], 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). Regarding 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 the best of 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 [51], 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 earlier. Furthermore, confirmed in our

study and in previous reports of patients with breast cancer [5, 70–73], a positive correlation exists between sleep disturbance and fatigue before CTX. Consistent with another study of patients with breast cancer [74], women who reported higher sleep disturbance experienced decrements in attentional function before 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 patients with breast cancer before [75], during [62, 73, 76], and after [76, 77] adjuvant CTX. Similarly, in one study [78], a relationship was found between disturbed sleep and increased anxiety in women before breast cancer surgery. In addition, although 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 [79]. Although 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 [79], the studies cited earlier included only patients with breast cancer. 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 before the initiation of CTX, changes in sleep disturbance before 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. Although 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. Information on the menopausal status of the women in this study is not available. Therefore, we cannot evaluate its influence on sleep disturbance. Finally, 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. On the basis of 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 before 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.

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Conflict of interest statement. None declared.

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