Distinct Sleep Disturbance and Cognitive Dysfunction Profiles in Oncology Outpatients Receiving Chemotherapy

by

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ABSTRACT

Background – Sleep disturbance and cancer-related cognitive impairment (CRCI) are two of the most common symptoms reported by patients undergoing chemotherapy. Less is known about how these symptoms co-occur and their associated risk factors.

Objective – Study purposes were to identify subgroups of patients with distinct sleep disturbance and CRCI profiles and evaluate for differences among the subgroups in demographic and clinical characteristics, symptom severity scores, and QOL outcomes.

Methods – A total of 1330 oncology outpatients receiving chemotherapy completed self-report questionnaires on sleep disturbance and cognitive dysfunction six times over two cycles of chemotherapy. Latent profile analysis was used to identify distinct sleep disturbance AND cognitive dysfunction profiles. Parametric and non-parametric tests were used to evaluate for differences among the classes.

Results – Two distinct profiles were identified (i.e., Low = low levels of both sleep disturbance and cognitive dysfunction (53.5%); High = high levels of both sleep disturbance and cognitive dysfunction (45.5%)). Patients in the High class were younger, more likely to be female, had a lower functional status and a higher level of comorbidity. In addition, these patients had a higher symptom burden and a lower quality of life.

Conclusion – Almost half of the patients undergoing chemotherapy experienced clinically meaningful levels of both symptoms.

Implications for Practice – Of note, sleep disturbance is frequently overlooked by both clinicians and patients. Clinicians need to recommend cognitive rehabilitation and physical activity programs to decrease patients' symptom burden.

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INTRODUCTION

Co-occurring symptoms are commonly experienced by oncology patients receiving chemotherapy. In a previous study by our research team,[1] 40% of the patients reported an average of 25 co-occurring symptoms. Of note, difficulty sleeping and difficulty concentrating were among the five most prevalent co-occurring symptoms. However, except for studies of symptom clusters,[2] these two symptoms are evaluated independently in oncology patients receiving chemotherapy.

Sleep disturbance is a common symptom that affects 30% to 88% of oncology patients.[3] This wide range in occurrence rates suggests a large amount of inter-individual variability in oncology patients experience with this symptom. Sleep disturbance results in poorer functional status, decrements in quality of life (QOL), and in some cases, disease progression.[4] In a recent meta-analysis,[4] demographic and clinical characteristics that were associated with higher levels of sleep disturbance included: older age, female gender identification, being unmarried, lower annual income, advanced cancer stage, and treatment with chemotherapy and/or radiation.

Cancer-related cognitive impairment (CRCI) is one of the most pervasive and feared adverse effects of chemotherapy.[5] Findings from one review suggest that over 75% of breast cancer patients experience CRCI during treatment and that in 35% to 60% of these patients, the symptom persists following the completion of chemotherapy.[6] The cognitive domains most impaired after chemotherapy are memory, processing speed, attention, and executive function.[7] CRCI negatively impacts cancer patients in a multitude of ways. As noted in two reviews,[7, 8] patients with CRCI reported challenges with daily functioning and decision-making; decreases in autonomy and self-confidence;

and difficulties with work, social relationships, and ability to adhere to treatment regimens. In addition, CRCI results in decreases in patients' QOL and survival.

A large amount of inter-individual variability exists in the development of and recovery from CRCI.[9] This heterogeneity suggests that the risk factors for this symptom are multifactorial. Findings from a variety of meta-analyses and systematic reviews have noted that the inter-individual variability in CRCI may be related to: age, level of education, race/ethnicity, occurrence of multiple comorbidities, cancer type, chemotherapy regimen, duration of treatment, co-occurring symptoms (e.g., anxiety, depression, fatigue, insomnia), and cognitive reserve.[6-12]

While most studies have evaluated risk factors for sleep disturbance and CRCI in oncology patients independently, emerging evidence suggests that sleep disturbance appears to be involved in the cellular and molecular mechanisms of cognitive decline.[13] In this systematic review of studies of patients with mild cognitive impairment,[13] compared to healthy older adults, patients with mild cognitive impairment had less total sleep time and lower sleep efficiency.

Across the various review articles of sleep disturbance[4, 12] and CRCI[6-12] in oncology patients, most of the previous cross-sectional and longitudinal studies had relatively small samples sizes; evaluated primarily women with breast cancer; did not include a comprehensive list of demographic and clinical characteristics as potential risk factors; and did not evaluate a comprehensive list of common symptoms associated with the administration of chemotherapy.[7] In addition, none of these studies used a person-centered analytic approach to model sleep disturbance AND CRCI together simultaneously and identify distinct joint symptom profiles. Therefore, the purposes of

this study, in a sample of oncology outpatients undergoing chemotherapy (n=1333), was to use latent profile analysis (LPA) to identify subgroups of patients with distinct sleep disturbance and CRCI profiles. In addition, differences among the subgroups in demographic and clinical characteristics, symptom severity scores, and QOL outcomes were evaluated.

PATIENTS AND METHODS

Patients and Settings

This longitudinal study, described in detail elsewhere,[14] evaluated the symptom experience of oncology outpatients receiving chemotherapy. Eligible 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 gave written informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's 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 most common reason for refusal was being overwhelmed with their cancer treatment.

Instruments

Demographic and clinical characteristics

A demographic questionnaire obtained information on age, gender, ethnicity, marital status, living arrangements, education, employment status, and income. In addition, patients completed the Karnofsky Performance Status (KPS) scale,[15] the Alcohol Use Disorders Identification Test (AUDIT),[16] and the Self-Administered

Comorbidity Questionnaire (SCQ).[17] The SCQ evaluates the occurrence, impact of, and treatment for 13 common medical conditions. Medical records were reviewed for disease and treatment characteristics.

Sleep disturbance and cognitive function measures

The 21-item General Sleep Disturbance Scale (GSDS) was designed to assess the quality of sleep in the past week. Each item was rated on a 0 (never) to 7 (everyday) numeric rating scale (NRS). The GSDS total score is the sum of the seven subscale scores that can range from 0 (no disturbance) to 147 (extreme sleep disturbance). Each mean subscale score can range from 0 to 7. Higher total and subscale scores indicate higher levels of sleep disturbance. Subscales scores of ≥3 and a GSDS total score of ≥43 indicate a significant level of sleep disturbance.[18] In this study, the Cronbach's alpha for the GSDS total score was 0.83.

The 16-item Attentional Function Index (AFI) assesses an individual's perceived effectiveness in performing daily activities that are supported by attention and working memory.[19] A higher total mean score on a 0 to 10 NRS indicates greater capacity to direct attention.[19] 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).[20] In addition, the AFI has three subscales (i.e., effective action, attentional lapses, interpersonal effectiveness). The AFI has well established reliability and validity.[19] In this study, the Cronbach's alpha for the total AFI score was 0.93.

Symptom Measures

The 20-item Center for Epidemiological Studies-Depression scale (CES-D) evaluates 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.[21-23] In this study, its Cronbach's alpha was 0.89.

The 20 items on each of the Spielberger State-Trait Anxiety Inventories (STAI-T and STAI-S) were rated from 1 to 4.[23] 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. The STAI-S and STAI-T inventories have well established validity and reliability.[24-26] In the current study, the Cronbach's alphas for the STAI-T and STAI-S were 0.92 and 0.96, respectively.

The 18-item Lee Fatigue Scale (LFS) was designed to assess physical fatigue and energy.[27] Each item was rated on a 0 to 10 NRS. Total fatigue and energy scores are 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) and energy (i.e., ≤6.2 for morning energy, ≤3.5 for evening energy).[18] It was chosen for this study because it is relatively short, easy to administer, and has well established validity and reliability.[27-32] 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.

Worst pain severity was assessed using the Brief Pain Inventory (BPI).[33] Patients were asked to indicate whether they were generally bothered by pain (yes/no). If they were generally bothered by pain, they rated their worst pain severity in the past 24 hours using a 0 (no pain) to 10 (worst pain imaginable) NRS.

QOL Scales

QOL was evaluated using general (i.e., Medical Outcomes Study-Short Form-12 (SF-12)) and disease specific (i.e., Quality of Life Scale-Patient Version (QOL-PV)) measures. The SF-12 consists of 12 questions about physical and mental health as well as overall health status. The individual items on the SF-12 are evaluated and the instrument is scored into two components, namely a physical component summary (PCS) score and a mental component summary (MCS) score. These scores can range from 0 to 100. Higher PCS and MCS scores indicate a better QOL. The SF-12 has well established validity and reliability.[34]

The QOL-PV is a 41-item instrument that assesses four dimensions of QOL (i.e., physical, psychological, social and spiritual well-being) in cancer patients, as well as a total QOL score. Each item was rated on a 0 to 10 NRS with higher scores indicating a better QOL. The QOL-PV has established validity and reliability.[35, 36]

Study Procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco and by the Institutional Review Board at each of the study sites. Eligible 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. Depending on the length of their chemotherapy cycles, patients completed questionnaires in their homes, a total of six times over two cycles of chemotherapy (i.e., prior to chemotherapy administration (i.e., recovery from previous cycle), approximately 1 week after chemotherapy administration (i.e., acute symptoms), approximately 2 weeks after chemotherapy administration (i.e., potential nadir)).

Data Analysis

Latent profile analysis (LPA) was used to identify subgroups of patients with distinct sleep disturbance **AND** cognitive function profiles. This LPA was done with the combined set of variables over time (i.e., using the GSDS and AFI 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. The LPA was done using Mplus version 8.4.[37]

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., GSDS and AFI 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.[38] Model fit was evaluated to identify the

solution that best characterized the observed latent class structure with the Bayesian Information Criterion (BIC),[39] Vuong-Lo-Mendell-Rubin likelihood ratio test (VLRM), entropy, and latent class percentages that were large enough to be reliable.[40] Missing data were accommodated for with the use of the Expectation-Maximization (EM) algorithm.[41]

Data were analyzed using SPSS version 27 (IBM Corporation, Armonk, NY). Descriptive statistics and frequency distributions were calculated for demographic and clinical characteristics. Differences among the sleep disturbance AND cognitive function classes in demographic, clinical, and symptom characteristics and QOL outcomes were evaluated using parametric and nonparametric tests. A p-value of <0.05 was considered statistically significant.

RESULTS

Latent Classes for Sleep Disturbance and Cognitive Function

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

The sleep disturbance and cognitive function classes were labeled as low sleep disturbance and high cognitive function (i.e., Low = low levels of both sleep disturbance and cognitive dysfunction) and high sleep disturbance and low-to-moderate cognitive function (High = High levels of both sleep disturbance and cognitive dysfunction) based

on clinically meaningful cut-off scores for sleep disturbance and cognitive dysfunction. As shown in Figure 1, for both classes, sleep disturbance increased and cognitive function decreased in the weeks following the administration of chemotherapy (i.e., assessments 2 and 5).

Differences in Demographics and Clinical Characteristics

Compared to the Low class, patients in the High class were younger, had fewer years of education, were more likely to be female, less likely to be married/partnered, more likely to live alone, more likely to be unemployed, more likely to have a lower annual household income, and more likely to have childcare responsibilities (Table 2).

In terms of clinical characteristics, compared to the Low class, patients in the High class had lower KPS scores, a higher number of comorbidities, a higher SCQ score, a higher MAX2 score, were less likely to exercise on a regular basis and were less likely to have gastrointestinal cancer. In addition, patients in the High class were more likely to self-report a diagnosis of heart disease, lung disease, ulcer or stomach disease, anemia or blood disease, depression, and back pain and were less likely to receive a chemotherapy regimen with a targeted therapy (Table 2).

Differences in Sleep Disturbance and Cognitive Function

Compared to the Low class, patients in the High class had significantly higher GSDS subscale and total scores. In addition, patients in the High class had significantly lower AFI subscale and total scores. (Table 3).

Differences in Co-occurring Symptom Severity

Compared to the Low class, patients in the High class had significantly higher depressive symptoms, trait and state anxiety, morning and evening fatigue, worst pain,

and pain interference scores. In addition, patients in the High class had significantly lower morning and evening energy scores. Compared to the Low class, patients in the High class were more likely to report the occurrence of both cancer and non-cancer pain and were less likely not to have pain (Table 4).

Differences in QOL Outcomes

Compared to the Low class, patients in the High class reported significantly lower scores for all subscales on the SF-12, as well as for the PCS and MCS scores. Except for the spiritual well-being subscale, patients in the High class reported significantly lower scores for all MQOLS-PV subscales as well as total score (Table 5).

DISCUSSION

This study is the first to identify subgroups of patients with distinct co-occurring sleep disturbance and cognitive dysfunction profiles. Compared to previous prevalence rates reported for sleep disturbance (i.e., 30% to 88%[3]) and CRCI (i.e., 35% to 75%[6]), almost half of our sample (45.5%) had very high levels of sleep disturbance and clinically meaningful decrements in cognitive function. Consistent with previous reports of sleep disturbance[42] and CRCI[43] as single symptoms, the pattern of change in symptom severity was similar in both classes. The significant increases in sleep disturbance and cognitive dysfunction following the administration of chemotherapy with subsequent recovery suggests additive or synergistic relationships between these two co-occurring symptoms.

Characteristics of Sleep Disturbance and CRCI

In terms of sleep disturbance, while the total GSDS scores for the Low class approached the clinically meaningful cutoff score of $\geq$43, patients in the High class had

scores that were worse than those reported by post-partum mothers (55.5).[28] Of note, the DSM-V defines a diagnosis of insomnia as “a predominant complaint of dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms (i.e., difficulty initiating sleep; difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings; early-morning awakening with inability to return to sleep)” that occurs at least 3 nights per week, is present for at least 3 months, and has a negative impact on important areas of function.[44] While only evaluated for approximately two months (i.e., over two cycles of chemotherapy) in this study, patients in the High class had problems with both the initiation (i.e., sleep onset latency) and maintenance (i.e., mid-sleep awakenings, early awakenings) of sleep that occurred on greater than three days per week. In contrast, patients in the Low class primarily had problems with sleep maintenance. Both groups of patients warrant clinical evaluation because sleep disturbance may reflect disruptions in circadian functions that may result in decreases in the efficacy of chrono-modulated chemotherapy[45] and overall survival.[46]

In terms of CRCI, the total AFI scores reported by the patients in the High class were in the low category for this measure. This self-report measure focuses on an evaluation of an individual’s perceived effectiveness in performing common activities that require attention and working memory with a particular emphasis on one’s ability to plan, carry out activities, and function effectively in daily life.[19] While exact cutoff scores are not established for the subscales of the AFI, all of these scores were in the low-to-moderate range. The effective action subscale focuses on an evaluation of an individual’s ability to get started with activities, make decisions, and maintain attention

on various tasks. The identification of patients with low scores on this subscale should prompt an evaluation of their ability to perform routine activities of daily living as well as carry out employment and family responsibilities. Given that the attentional lapses subscale focuses on memory and concentration, patients in the High class may have challenges with the retention of information, which can have a negative impact on their adherence with care instructions (e.g., taking oral chemotherapy drugs, routine use of anti-emetics or pain medications).

The inclusion of the items on interpersonal effectiveness scale was based on cognitive theory that suggests that when attention is compromised, individuals experience a loss in the effectiveness of executive functioning which can lead to irritability and annoyance.[47] The poor interpersonal effectiveness scores in the High class may hinder them from benefiting from social relationships. These findings are consistent with two reviews that noted patients with CRCI report challenges with daily functioning, decision-making, work, social relationships, and ability to adhere to treatment regimens, that result in decreases in QOL and survival.[7, 8]

A growing body of evidence suggests that decrements in sleep quality are associated with decreases in cognitive function.[48-50] Several plausible hypotheses can explain this association. For example, in a study of patients with breast cancer who had completed chemotherapy,[51] significant correlations were found between amyloid beta-42, amyloid beta-40, tau, serum cytokines, and objective measures of cognitive function and self-reported sleep disturbance. The authors concluded that interactions may occur with inflammatory mediators and neurodegenerative processes that contribute to the severity of both symptoms. In addition, sleep disturbance may perpetuate CRCI by

causing increases in amyloid-β deposition, alterations in neurotransmitter systems, dysregulation of the hypothalamic-pituitary-adrenal axis, neuro-inflammation, and impaired hippocampal neurogenesis.[49] Equally important, unrelieved stress, concomitant use of medications (e.g., analgesics, corticosterioids), hormonal changes, and a higher comorbidity burden can contribute to higher levels of sleep disturbance and cognitive dysfunction.[9, 50] Given the additive or synergistic relationship between sleep disturbance and CRCI, it is fortunate that emerging evidence suggests that using techniques like cognitive behavioral therapy to improve sleep may result in concomitant improvements in cognitive function.[49]

Demographic and Clinical Characteristics

An evaluation of differences in demographic characteristics suggest that numerous social determinants of health are associated with a higher symptom burden. Specifically, patients in the High class were younger; were more likely to be unemployed; and had fewer years of education, a lower annual household income, and childcare responsibilities. In addition, they were more likely to not be married/partnered and to live alone (both possible proxies of social isolation). Except for age, all of these associations are consistent with previous reports for the individual symptoms.[4, 6-12] One potential explanation for these associations is that a lower socioeconomic status is associated with pervasive physical and psychological stressors that make these individuals more vulnerable to increases in allostatic load and associated sleep disturbance and cognitive impairments induced by cancer treatments.[9] The lack of both physical and emotional support, as well as social isolation during treatment, can further increase a patient's level of stress and lead to sleep disturbance and cognitive

dysfunction. Given that this study evaluated a very limited number of social determinants of health, future research needs to explore additional characteristics (e.g., neighborhood, food security, environmental exposures).[52]

While previous studies found an association between older age and higher levels of CRCI, as well as sleep disturbance,[4, 7, 8] patients in our High class were more likely to be younger. Of note, our finding is consistent with a study by the developers of the AFI who noted that younger individuals may react more strongly to small cognitive changes, while older individuals may have lower expectations, having adapted to alterations in cognition that accompany normal aging.[19] These inconsistent findings warrant investigation in future studies.

A comparison of differences in clinical characteristics between the two classes highlights the inter-relationships between these two symptoms and higher comorbidity burden and significant functional impairment. Specific comorbidities associated with membership in the High class included: heart disease, lung disease, ulcer or stomach disease, anemia or blood disease, depression, and back pain. While causal relationships warrant additional evaluation, these findings suggest that patients in the High class had less physical reserve during chemotherapy. Multiple potential explanations exist for these complex inter-relationships. Both sleep disturbance and CRCI,[53, 54] as well as a number of chronic conditions,[55] are associated with increases in inflammatory responses. In addition, stress and dysregulation of the hypothalamic-pituitary-adrenal axis may contribute to a higher symptom [56] and comorbidity [57] burden. Furthermore, the side effects of chemotherapy and medications used to treat various comorbid conditions may add to the symptom burden in the High class. The assertion

that the side effects of chemotherapy contribute to a higher symptom burden is supported by the fact that patients in the High class had a higher MAX2 score and were more likely to receive a standard chemotherapy regimen without a targeted therapy. The linkages between the higher symptom and comorbidity burden and lower functional status are supported by the finding that patients in the High class were less likely to exercise on a regular basis. It is not entirely clear why a lower percentage of patients in the High class had a diagnosis of gastrointestinal cancer. Taken together, our findings suggest that clinicians need to assess oncology patients for multiple comorbid conditions and ensure that these conditions are optimally managed during the receipt of chemotherapy.

Common Symptoms

Consistent with multiple meta-analyses and reviews of sleep disturbance[3] and CRCI,[7, 8] patients in the High class reported clinically meaningful levels of depressive symptoms, state and trait anxiety, morning and evening fatigue, pain, and decrements in morning and evening energy. These symptoms are often clustered together because they share common predisposing and precipitating factors (e.g., low physical activity; receipt of chemotherapy with associated release of pro-inflammatory cytokines).[2, 58] Unfortunately, these co-occurring symptoms often exacerbate each other and result in decrements in physical and social well-being. However, if high risk patients are identified, clinicians can recommend exercise, cognitive behavioral therapy, the use of positive coping skills, and/or increased social interaction, because these interventions demonstrated improvements in mood, fatigue, pain, cognition, and/or sleep.[59, 60]

QOL Outcomes

Unsurprising given the high symptom and comorbidity burden of the High class, except for spiritual well-being, these patients reported significantly lower QOL scores for all domains of QOL that were assessed using the general and disease-specific measures. Equally important, the PCS and MCS scores of these patients were well below the normative score of 50 for the general population of the United States.[34]

Limitations

While this study had a large sample size, given that it was homogenous in terms of race/ethnicity and socioeconomic status, additional research with more diverse samples and a more comprehensive list of social determinants of health is warranted. In addition, despite assessments over two cycles of chemotherapy, pretreatment and post-treatment assessments are necessary to obtain a more detailed understanding of the trajectories of both symptoms. As both sleep disturbance and CRCI were assessed using self-report measures, future studies need to use objective measures of both symptoms, as well as extend assessment of CRCI beyond attention and executive function. Future research expanding on the findings of this study should also investigate optimal assessment tools in practice and effective interventions, as well as explore underlying mechanisms of symptoms separately and together to elucidate causation. This includes inflammatory markers, concomitant medication use, stress, resiliency, genetics and epigenetics.

CLINICAL IMPLICATIONS

Given the severity of both sleep disturbance and CRCI in our High class, these two symptoms, as well as the other common symptoms, warrant management. While one cannot demonstrate causality, sleep disturbance is one of the major risk factors for mild cognitive impairment, and there is growing support for a bidirectional relationship.[49] One could hypothesize that the assessment and management of sleep disturbance may decrease the severity of the other co-occurring symptoms. Of note, sleep disturbance is frequently overlooked by both clinicians and patients.[61, 62] Perhaps assumed to be a normal and temporary reaction to a cancer diagnosis and/or its treatment(s), sleep disturbance is rarely included in routine screening. An assessment of CRCI is challenging given the lack of routine, standardized, brief and accurate neuropsychological tests. In addition, this study discovered potentially modifiable demographic characteristics (e.g., social isolation) and clinical characteristics (e.g., lack of regular exercise) associated with a worse sleep disturbance and cognitive dysfunction trajectory. Patients and clinicians would benefit from a better understanding of risk factors, possible adverse effects, and impact of these two symptoms on QOL prior to the initiation of treatment. Mindful assessment and formulation of an appropriate patient-centered care plan for both symptoms are vital to improving patients' adherence with treatment and QOL. The most promising strategies are cognitive rehabilitation and physical activity programs.

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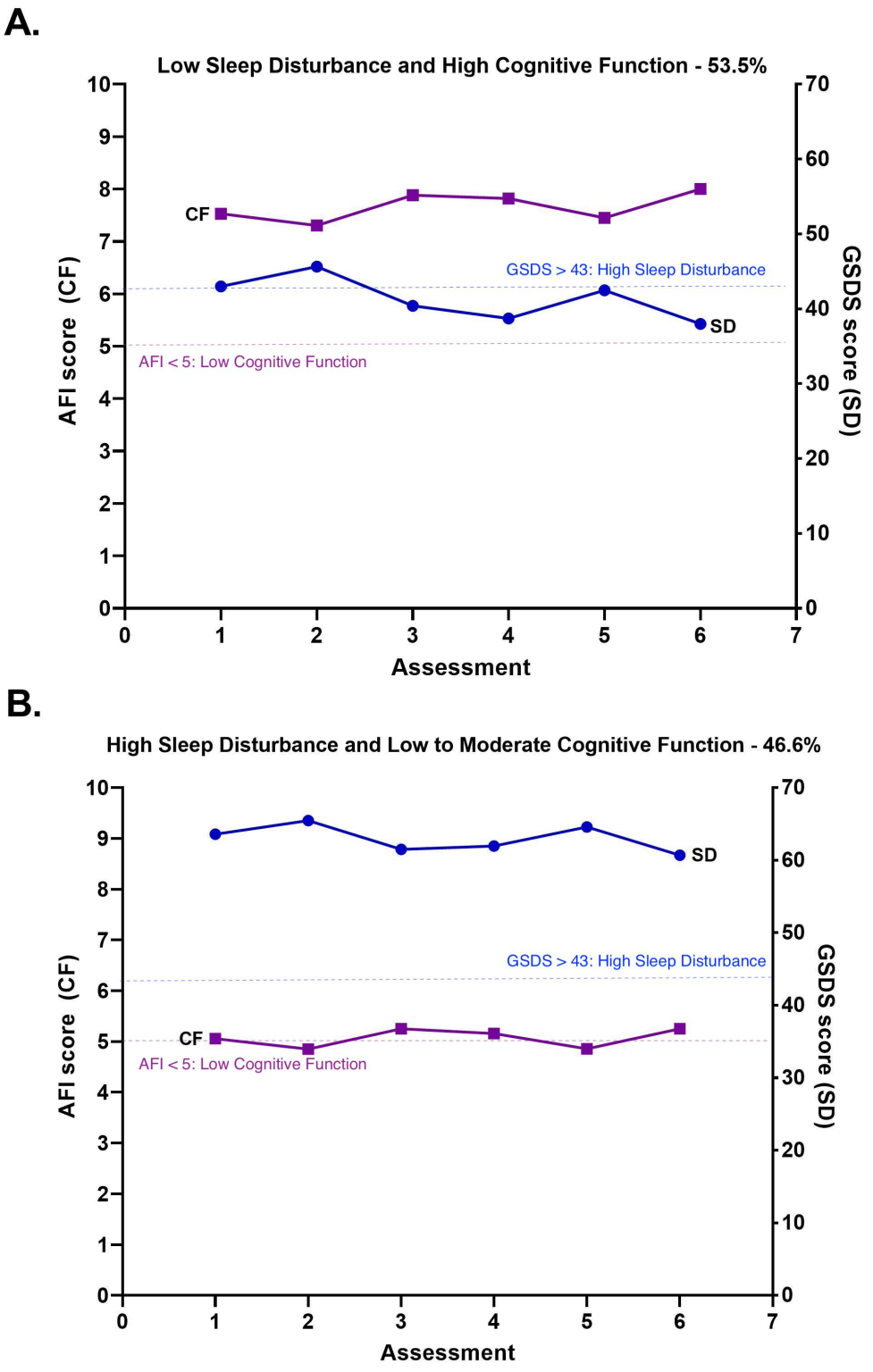

Figure 1 – Sleep disturbance and cognitive function trajectories in the two latent patient classes over two cycles of chemotherapy: Low symptom class (A) and High symptom class (B).

Table 1 – General Sleep Disturbance Scale and Attentional Fatigue Index Scores Over Six Assessments: Latent Profile Solutions and Fit Indices for One through Three Classes

Model	LL	AIC	BIC	Entropy	VLMR
1 Class	-39516.08	79148.15	79449.47	n/a	n/a
2 Class[a]	-38746.11	77634.22	78003.08	0.78	1539.93 ‡
3 Class	-38476.67	77121.34	77557.74	0.78	ns

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

‡$p < .00005$

[a] The 2-class solution was selected because the BIC for that solution was lower than the BIC for the 1-class solution. In addition, the VLMR was significant for the 2-class solution, indicating that two classes fit the data better than one class. Although the BIC was smaller for the 3-class than for the 2-class solution, the VLMR was not significant for the 3-class solution, indicating that too many classes were extracted.

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 Between the Sleep Disturbance and Cognitive Function Classes

Characteristics	Low Sleep Disturbance and High Cognitive Function (0) 53.5% (n=713)	High Sleep Disturbance and Low to Moderate Cognitive Function (1) 45.5% (n=620)	Statistics
	Mean (SD)	Mean (SD)	
Age (years)	58.2 (11.8)	55.9 (12.9)	t = 3.34, p = .001
Education (years)	16.4 (3.0)	16.0 (3.0)	t = 2.56, p = .011
Body mass index (kg/m^2)	26.0 (5.3)	26.4 (6.0)	t = -1.34, p = .181
Karnofsky Performance Status score	84.2 (11.2)	75.1 (12.1)	t = 13.85, p <.001
Number of comorbidities out of 13	2.2 (1.3)	2.7 (1.5)	t = -6.42, p <.001
Self-Administered Comorbidty Questionnaire score	4.8 (2.7)	6.3 (3.5)	t = -8.78, p <.001
Alcohol Use Disorders Identification Test score	2.9 (2.1)	3.1 (2.9)	t = -1.54, p = .125
Time since cancer diagnosis (years)	2.0 (3.7)	2.0 (4.1)	U, p = .158
Time since cancer diagnosis (median)	0.41	0.44	
Number of prior cancer treatments	1.5 (1.5)	1.7 (1.5)	t = -1.45, p = .146
Number of metastatic sites including lymph node involvement	1.3 (1.2)	1.2 (1.2)	t = 0.21, p = .834
Number of metastatic sites excluding lymph node involvement	0.8 (1.0)	0.8 (1.1)	t = 0.37, p = .712
MAX2 score	0.17 (0.08)	0.18 (0.08)	t = -2.58, p = .010
	% (n)	% (n)	
Female (% yes)	73.2 (522)	83.4 (516)	FE, p <.001
Ethnicity			
White	69.0 (486)	70.1 (429)	
Asian or Pacific Islander	12.9 (91)	12.1 (74)	X^2 = 5.83, p = .120
Black	8.5 (60)	5.7 (35)	
Hispanic, Mixed, or Other	9.5 (67)	12.1 (74)	
Married or partnered (% yes)	69.6 (489)	58.6 (358)	FE, p <.001
Lives alone (% yes)	18.5 (130)	25.1 (154)	FE, p = .004
Childcare responsibilities (% yes)	19.7 (137)	25.0 (152)	FE, p = .023
Care of adult responsibilities (% yes)	6.6 (43)	9.4 (53)	FE, p = .087
Currently employed (% yes)	42.1 (296)	27.1 (167)	FE, p <.001
Annual household income			
<$30,000+	11.7 (73)	25.9 (147)	U, p <.001
$30,000 to <$70,000	20.3 (127)	22.0 (125)	0 > 1
$70,000 to <$100,000	18.5 (116)	15.2 (86)	
>$100,000	49.5 (310)	36.9 (209)	
Specific comorbidities (% yes)			
Heart disease	4.5 (32)	7.1 (44)	FE, p = .044
High blood pressure	31.0 (221)	29.2 (181)	FE, p = .511
Lung disease	9.4 (67)	13.5 (84)	FE, p = .019
Diabetes	8.8 (63)	9.0 (56)	FE, p = .923
Ulcer or stomach disease	3.6 (26)	6.3 (39)	FE, p = .030
Kidney disease	1.0 (7)	1.9 (12)	FE, p = .168
Liver disease	7.0 (50)	5.8 (36)	FE, p = .434
Anemia or blood disease	10.1 (72)	14.8 (92)	FE, p = .009
Depression	10.1 (72)	29.8 (185)	FE, p <.001
Osteoarthritis	10.8 (77)	13.5 (84)	FE, p = .130
Back pain	18.4 (131)	34.2 (212)	FE, p <.001
Rheumatoid arthritis	2.9 (21)	3.4 (21)	FE, p = .754
Exercise on a regular basis (% yes)	74.9 (526)	66.1 (397)	FE, p <.001
Current or history of smoking (% yes)	33.0 (233)	37.8 (229)	FE, p = .082

Characteristics	Low Sleep Disturbance and High Cognitive Function (0) 53.5% (n=713)	High Sleep Disturbance and Low to Moderate Cognitive Function (1) 45.5% (n=620)	Statistics
	% (n)	% (n)	
Cancer diagnosis			X^2 = 11.26, p = .010
Breast	38.4 (274)	42.6 (264)	NS
Gastrointestinal	34.4 (245)	26.0 (161)	0 > 1
Gynecological	16.0 (114)	19.0 (118)	NS
Lung	11.2 (80)	12.4 (77)	NS
Type of prior cancer treatment			
No prior treatment	26.4 (182)	23.5 (143)	
Only surgery, CTX, or RT	41.9 (289)	41.9 (255)	X^2 = 2.92, p = .405
Surgery & CTX, or Surgery & RT, or CTX & RT	19.9 (137)	19.9 (121)	
Surgery & CTX & RT	11.9 (82)	14.6 (89)	
Metastatic sites			
No metastasis	32.1 (226)	32.9 (201)	
Only lymph nodes	21.3 (150)	22.6 (138)	X^2 = 0.75, p = .862
Only non-lymph nodes	21.8 (154)	20.3 (124)	
Lymph nodes and other sites	24.8 (175)	24.2 (148)	
Chemotherapy regimen			X^2 = 7.12, p = .028
Only CTX	66.9 (468)	73.6 (446)	0 < 1
Only targeted therapy	3.4 (24)	2.5 (15)	NS
Both CTX and targeted therapy	29.7 (208)	23.9 (145)	0 > 1
Cycle length			
14-day cycle	44.2 (314)	39.3 (240)	U, p = .121
21-day cycle	48.5 (345)	53.4 (326)	
28-day cycle	7.3 (52)	7.2 (44)	
Emetogenicity of the CTX regimen			
Minimal/low	18.7 (133)	20.5 (125)	U, p = .898
Moderate	62.9 (447)	58.9 (360)	
High	18.4 (131)	20.6 (126)	
Antiemetic regimen			
None	7.6 (53)	6.6 (39)	
Steroid alone or serotonin antagonist alone	20.4 (142)	20.7 (123)	X^2 = 0.95, p = .814
Serotonin antagonist and steroid	48.1 (335)	47.2 (281)	
NK-1 receptor antagonist and two other antiemetics	23.9 (166)	25.5 (152)	

Abbreviations: CTX = chemotherapy, kg = kilograms, m^2 = meter squared, NK = neurokinin, NS = not significant, RT = radiation therapy, SD = standard deviation, U = Mann Whitney U test

+Reference group

Table 3 – Differences Between the Sleep Disturbance and Cognitive Function Classes in Attentional Function Index and General Sleep Disturbance Scale Scores at Enrollment

Symptoms[a]	Low Sleep Disturbance and High Cognitive Function 53.5% (n=713)	High Sleep Disturbance and Low to Moderate Cognitive Function 45.5% (n=620)	Statistics
	Mean (SD)	Mean (SD)	
Attentional Function Index (AFI)			
Effective action subscale	7.4 (1.6)	4.6 (1.7)	t = 30.57, p <.001
Attentional lapses subscale	7.7 (1.7)	5.4 (1.8)	t = 24.06, p <.001
Interpersonal effectiveness subscale	7.8 (1.5)	5.6 (1.9)	t = 23.86, p <.001
AFI total score (<5.0 = low, 5>0 to 7.5 = moderate, >7.5 = high)	7.6 (1.2)	5.0 (1.4)	t = 35.26, p <.001
General Sleep Disturbance Scale (GSDS)			
Quality of sleep (≥3.0)	2.7 (1.6)	4.0 (1.6)	t = -15.04, p <.001
Quantity of sleep (≥3.0)	4.4 (1.5)	4.9 (1.7)	t = -5.22, p <.001
Sleep onset latency (≥3.0)	2.0 (2.0)	3.6 (2.2)	t = -13.47, p <.001
Mid-sleep awakenings (≥3.0)	4.6 (2.3)	5.2 (2.0)	t = -4.19, p <.001
Early awakenings (≥3.0)	3.0 (2.4)	4.3 (2.3)	t = -9.32, p <.001
Medications for sleep (≥3.0)	0.5 (0.7)	0.8 (0.89)	t = -8.45, p <.001
Excessive daytime sleepiness (≥3.0)	1.9 (1.2)	3.4 (1.3)	t = -21.49, p <.001
GSDS total score (≤43.0)	42.8 (17.0)	63.7 (17.7)	t = -21.56, p <.001

Abbreviations: NS = not significant, SD = standard deviation

[a]Clinically meaningful cutoff scores

Table 4 – Differences in Co-occurring Symptom Severity Scores Between the Sleep Disturbance and Cognitive Function Classes

Symptoms[a]	Low Sleep Disturbance and High Cognitive Function 53.5% (n=713)	High Sleep Disturbance and Low to Moderate Cognitive Function 45.5% (n=620)	Statistics
	Mean (SD)	Mean (SD)	
Depressive symptoms (≥16)	8.2 (6.4)	18.4 (10.1)	t = -21.42, p <.001
Trait anxiety (≥31.8)	30.3 (7.7)	40.8 (10.5)	t = -20.11, p <.001
State anxiety (≥32.2)	29.0 (9.4)	40.0 (13.0)	t = -16.74, p <.001
Morning fatigue (≥3.2)	2.0 (1.8)	4.4 (2.1)	t = -21.64, p <.001
Evening fatigue (≥5.6)	4.6 (2.1)	6.1 (1.9)	t = -13.48, p <.001
Morning energy (≤6.2)	4.9 (2.4)	3.8 (1.9)	t = 9.45, p <.001
Evening energy (≤3.5)	3.9 (2.0)	3.2 (2.0)	t = 6.03, p <.001
Types of pain			X^2 = 89.58, p <.001
None	35.3 (248)	18.3 (111)	0 > 1
Only non-cancer pain	26.9 (189)	25.6 (155)	NS
Only cancer pain	17.6 (124)	13.7 (83)	NS
Both non-cancer and cancer pain	20.2 (142)	42.3 (256)	0 < 1
Worst pain intensity score	5.5 (2.5)	6.6 (2.4)	t = -6.03, p <.001
Mean pain interference score	2.2 (2.1)	3.9 (2.6)	t = -11.14, p <.001

Abbreviations: NS = not significant, SD = standard deviation

[a]Clinically meaningful cutoff scores

Table 5 – Differences Between the Sleep Disturbance and Cognitive Function Classes in General and Disease Specific Quality of Life Domains at Enrollment

Domains	Low Sleep Disturbance and High Cognitive Function 53.5% (n=713)	High Sleep Disturbance and Low to Moderate Cognitive Function 45.5% (n=620)	Statistics
	Mean (SD)	Mean (SD)	
Medical Outcomes Study – Short Form 12			
Physical functioning	62.7 (33.8)	40.4 (31.1)	t = 12.25, p <.001
Role physical	65.5 (26.9)	36.8 (24.3)	t = 20.18, p <.001
Bodily pain	85.0 (22.0)	64.7 (31.1)	t = 13.30, p <.001
General health	69.3 (25.2)	54.7 (29.1)	t = 9.57, p <.001
Vitality	56.9 (23.9)	31.9 (23.9)	t = 18.76, p <.001
Social functioning	78.2 (26.2)	53.8 (30.2)	t = 15.34, p <.001
Role emotional	87.2 (20.0)	62.0 (28.5)	t = 18.12, p <.001
Mental health	80.1 (16.2)	62.3 (21.5)	t = 16.62, p <.001
Physical component summary score	44.5 (10.0)	37.5 (10.0)	t = 12.34, p <.001
Mental component summary score	53.6 (7.7)	43.6 (10.7)	t = 18.61, p <.001
Multidimensional Quality of Life Scale – Cancer			
Physical well-being	7.4 (1.5)	5.7 (1.6)	t = 20.19, p <.001
Psychological well-being	6.3 (1.7)	4.6 (1.6)	t = 18.53, p <.001
Social well-being	6.5 (1.8)	4.8 (1.9)	t = 17.41, p <.001
Spiritual well-being	5.6 (2.1)	5.3 (2.0)	t = 1.96, p = .050
Total quality of life score	6.4 (1.2)	4.9 (1.3)	t = 21.01, p <.001

Abbreviation: SD = standard deviation

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