Title
Modifiable and Nonmodifiable Characteristics of Sleep Disturbance in Oncology Outpatients During Chemotherapy

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Modifiable and Nonmodifiable Characteristics Associated With Sleep Disturbance in Oncology Outpatients During Chemotherapy

by

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Modifiable and Nonmodifiable Characteristics of Sleep Disturbance in Oncology Outpatients During Chemotherapy

Sueann Mark

ABSTRACT

Study Objectives: In a sample of outpatients with breast, gastrointestinal (GI), gynecological (GYN), and lung cancer who received two cycles of chemotherapy (CTX) the purposes were to: evaluate for inter-individual differences in the severity of sleep disturbance and to determine which demographic, clinical, and symptom characteristics were associated with initial levels as well as the trajectories of sleep disturbance.

Methods: This study is part of a larger, longitudinal study of the symptom experience of oncology outpatients receiving CTX. A total of 1,331 patients completed study questionnaires in their homes, at six time points over two cycles of CTX (prior to CTX administration, approximately 1 week after CTX administration, and approximately 2 weeks after CTX administration). Questionnaires included demographic, clinical, and symptom assessments (i.e., General Sleep Disturbance Scale, Lee Fatigue Scale, Center for Epidemiological Studies-Depression Scale, Spielberger State-Trait Anxiety Inventories, Attentional Function Index).

Results: Hierarchical linear modeling based on full maximum likelihood estimation was performed. Characteristics associated with higher initial levels of sleep disturbance included: higher body mass index, poorer functional status, higher trait anxiety, higher depressive symptoms, and higher evening fatigue. Characteristics associated with the worse trajectories of sleep disturbance were higher levels of education and higher sleep disturbance. Characteristics associated with both higher initial levels and worse trajectories of sleep disturbance were higher morning fatigue and worse attentional function.

Conclusions: A great deal of inter-individual variability exists in sleep disturbance during CTX. The modifiable and non-modifiable characteristics found in this study can be used to identify higher risk patients and provide earlier interventions to reduce sleep disturbance.
Key words: sleep disturbance; chemotherapy; hierarchical linear modeling; fatigue; depression, anxiety; cancer

Table of Contents

List of Tables

List of Figures

Introduction

Sleep disturbance in oncology patients is estimated to be twice that of the general population. In addition, oncology patients with sleep disturbance report higher levels of fatigue and depression, increases in vasomotor/endocrine symptoms, and poorer quality of life (QOL). (for reviews see (1, 2)) Of note, in primarily cross-sectional studies, a number of demographic (i.e., age, gender, race), lifestyle (i.e., poor sleep hygiene, caffeine and alcohol consumption, smoking), psychological (i.e., depression, anxiety, worry or stress), and disease- (i.e., pain, activity/rest, hormone secretion, cytokine production) and treatment- (i.e., CTX, biotherapy, radiotherapy, and medication use) related factors were associated with increased levels of sleep disturbance (for review see (3)). Based on these findings, professional organizations, like the Oncology Nursing Society, identified sleep disturbance as a research priority.(4, 5)

While chemotherapy (CTX) is a common treatment for oncology patients, research on sleep disturbance during this treatment is limited. In a 2010 meta-synthesis that summarized 10 cross-sectional and 9 longitudinal studies on sleep disturbance in women with breast cancer who received CTX,(6) the studies included in this review had relatively small sample sizes; were limited to patients with breast cancer; did not evaluate predictors of sleep disturbance; and assessed a limited number of time points.(6) In terms of changes in sleep disturbance during CTX, the findings from this review were inconsistent. While some studies found that sleep disturbance increased over time, others showed no significant changes. These inconsistencies may be related to differences in the instruments used to assess sleep disturbance, as well as in the timing of assessments. In a recent longitudinal study that was not included in the reviews cited above,(3, 6) sleep disturbance was assessed prior to, during, and after CTX, in a sample of 80 patients with breast cancer.(7) Higher levels of sleep disturbance were associated with higher fatigue and depression scores at each time point. However, this study had a relatively small sample size, a low participation rate, and evaluations were done at only 3 time points (i.e.,

3-14 days before the initiation of CTX, one to 7 days prior to beginning cycle 4, and 6 months following the initiation of CTX).(7)

Given the paucity of research on changes in and predictors of sleep disturbance in patients with other cancer diagnoses receiving CTX, the purposes of our study, in a sample of outpatients with breast, gastrointestinal (GI), gynecological (GYN), and lung cancer who received two cycles of CTX (n=1331) were to evaluate for inter-individual differences in the severity of sleep disturbance and to determine which demographic, clinical, and symptom characteristics were associated with initial levels as well as the trajectories of sleep disturbance.

Methods

Patients and Settings

This study is part of a larger, longitudinal study of the symptom experience of oncology outpatients receiving CTX.(8-13) Eligible patients were ≥18 years of age; had a diagnosis of breast, GI, GYN, or lung cancer; had received CTX within the preceding four weeks; were scheduled to receive at least two additional cycles of CTX; were able to read, write, and understand English; and gave written informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs.

Instruments

A demographic questionnaire obtained information on age, gender, ethnicity, marital status, living arrangements, education, employment status, and income. Medical records were reviewed for disease and treatment characteristics.

Karnofsky Performance Status (KPS) scale is widely used to evaluate functional status in patients with cancer and has well-established validity and reliability.(14) Patients rated their functional status using the 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).(14, 15)

Self-Administered Comorbidity Questionnaire (SCQ) consists of 13 common medical conditions simplified into language that can be understood without prior medical knowledge.(16) Patients indicated if they had the condition; if they received treatment for it (proxy for disease severity); and if it limited their activities (indication of functional limitations). For each condition, the patient can receive a maximum of 3 points. The total SCQ score ranges from 0 to 39. The SCQ has well-established validity and reliability.(17, 18)

Alcohol Use Disorders Identification Test (AUDIT) is a 10-item questionnaire that assesses alcohol consumption, alcohol dependence, and the consequences of alcohol abuse in the last 12 months. The AUDIT gives a total score that ranges between 0 and 40. Scores of ≥8 are defined as hazardous use and scores of ≥16 are defined as use of alcohol that is likely to be harmful to health.(19, 20) The AUDIT has well-established validity and reliability.(21-23) In this study, its Cronbach's alpha was 0.63.

General Sleep Disturbance Scale (GSDS) consists of 21 items 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 $\geq$3 and a GSDS total score of $\geq$43 indicate a significant level of sleep disturbance.(24) The GSDS has well-established validity and reliability.(25-27) In the current study, the Cronbach's alpha for the GSDS total score was 0.83.

Lee Fatigue Scale (LFS) consists of 18 items designed to assess physical fatigue and energy.(28) 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) (24) and energy (i.e., ≥6.2 for morning energy, ≥3.5 for evening energy).(24) 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.

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-T measures a person's predisposition to anxiety as part of one's personality. 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. Cutoff scores of ≥31.8 and ≥32.2 indicate high levels of trait and state anxiety, respectively. The STAI-T and STAI-S inventories have well-established validity and reliability.(33-35) In the current study, the Cronbach's alphas for the STAI-T and STAI-S were 0.92 and 0.96, respectively.

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

Attentional Function Index (AFI) consists of 16 items designed to measure attentional function.(39) A higher total mean score on a 0 to 10 NRS indicates greater capacity to direct attention.(39) 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).(40) The AFI has well-established reliability and validity.(39) In this study, the Cronbach's alpha for the total AFI score was 0.93.

The occurrence of pain was evaluated using the Brief Pain Inventory.(41) 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.

Study Procedures

The study was approved by the Institutional Review Board at each of the study sites. Eligible patients were approached in the infusion unit by a member of the research team to discuss participation in the study. Written informed consent was obtained from all patients. Depending on the length of their CTX cycles (i.e., 14-day, 21-day, or 28-day), patients completed study questionnaires in their homes, a total of six times over two cycles of CTX (prior to CTX administration (i.e., recovery from previous CTX cycle; assessments 1 and 4), approximately 1 week after CTX administration (i.e., acute symptoms; assessments 2 and 5), and approximately 2 weeks after CTX administration (i.e., potential nadir; assessments 3 and 6)).

Data Analyses

Descriptive statistics and frequency distributions were generated on the sample characteristics and symptom severity scores at enrollment using the Statistical Package for the Social Sciences (SPSS) version 22.(42)

Hierarchical Linear Modeling (HLM) based on full maximum likelihood estimation was performed in two stages using software developed by Raudenbush and Bryk.(43) The HLM methods are described in detail elsewhere.(31, 44-47) In brief, during stage 1, intra-individual variability in sleep disturbance over time was examined. A piecewise model strategy was employed to evaluate the pattern of change in sleep disturbance over time because the six assessments encompassed two cycles of CTX. The six assessments were coded into two pieces. Assessments 1, 2, and 3 comprised the first piece (PW1) that was used to model changes over time in sleep disturbance during the first CTX cycle. Assessments 4, 5, and 6 comprised the second piece (PW2) that was used to model changes over time during the

second CTX cycle. A piecewise model can be more sensitive to the timing and sequencing of changes in a dependent variable than conventional HLM models that would have assessed linear, quadratic, or cubic changes over the six assessments and would not have paid attention to the two different CTX cycles.(48)

The second stage of the HLM analysis examined inter-individual differences in the piecewise trajectories of sleep disturbance by modeling the individual change parameters (i.e., intercept and slope parameters) as a function of proposed predictors at level 2. Supplementary Table 1 lists the potential predictors that were developed based on a review of the literature on sleep disturbance in oncology patients undergoing CTX.

To improve estimation efficiency and construct a parsimonious model, exploratory level 2 analyses were completed in which each potential predictor was assessed to determine whether it would result in a better fitting model if it alone were added as a level 2 predictor. Predictors with a *t* value of <2.0 were excluded from subsequent model testing (see Supplementary Table 1). All potential significant predictors from the exploratory analyses were entered into the model to predict each individual change parameter. Only predictors that maintained a statistically significant contribution in conjunction with other predictors were retained in the final model. A *p*-value of <.05 indicates statistical significance.

Results

Sample Characteristics

The demographic, clinical, and symptom characteristics of the sample (N=1331) are presented in Table 1. The sample was predominately female (78%, n = 1038) with a mean age of 57 (±12.4) years. The patients had an average of 16 (±3.0) years of education, a BMI of 26.16 (±5.62), and a KPS score of 80.00 (±12.40). The patients were 1.90 (±3.87) years from their cancer diagnosis (median = 0.42), primarily being treated with 21-day CTX cycles (51%), and had one metastatic site. At enrollment, the mean scores on the GSDS, STAI-T, and STAI-S were above the cut-off scores for clinically meaningful levels for sleep disturbance, trait anxiety,

and state anxiety, respectively. In addition, the mean evening energy LFS score was below the clinically meaningful cutoff.

Table 1. Demographic, Clinical, and Symptom Characteristics of the Patients (n=1331)

Demographic Characteristics	
Age (years; mean (SD))	57.18 (12.39)
Gender (% female (n))	78 (1038)
Ethnicity (% (n))	
White	69.5 (925)
Black	9.8 (131)
Asian/Pacific Islander	9.6 (128)
Hispanic/Mixed/Other	11.0 (147)
Education (years; mean (SD))	16.18 (2.98)
Married or partnered (% yes (n))	65.0 (865)
Lives alone (% yes (n))	21.3 (283)
Currently employed (% yes (n))	34.6 (461)
Child care responsibilities (% yes (n))	21.7 (289)
Income (% yes (n))	
Less than $30,000	18.5 (220)
$30,000 to <$70,000	21.2 (252)
$70,000 to < $100,000	16.9 (201)
More than $100,000	43.5 (518)
Clinical Characteristics	
Number of comorbidities (mean (SD))	2.40 (1.44)
Self-administered Comorbidity Questionnaire score (mean (SD))	5.48 (3.20)
Body mass index (kg/m^2; mean (SD))	26.16 (5.62)
Hemoglobin (gm/dL; mean (SD))	11.54 (1.43)
Karnofsky Performance Status score (mean (SD))	80.00 (12.40)
Have you ever considered yourself a smoker (% yes (n)	34.8 (463)
Exercise on a regular basis (% yes (n))	71.5 (951)
Specific comorbidities reported (% yes (n))	
High blood pressure	30.2 (402)
Back pain	25.7 (342)
Depression	19.3 (257)
Osteoarthritis	12.1 (161)
Anemia or blood disease	12.3 (164)
Lung disease	11.3 (151)
Diabetes	8.9 (119)
Liver disease	6.5 (86)
Heart disease	5.7 (76)
Rheumatoid arthritis	3.2 (42)
Ulcer or stomach disease	4.9 (65)
Kidney disease	1.4 (19)
Cancer diagnosis (% yes (n))	
Breast	40.3 (537)
Gastrointestinal	29.8 (397)
Gynecological	17.7 (235)
Lung	12.2 (162)
Time since cancer diagnosis (years; mean (SD))	1.97 (3.87)

Time since cancer diagnosis (years; median)	0.42
Any prior cancer treatments (% yes (n))	75.6 (1006)
Number prior cancer treatments (mean (SD))	1.59 (1.50)
Chemotherapy cycle length (% (n))	
14 days	41.7 (555)
21 days	51.0 (679)
28 days	7.3 (97)
Presence of metastatic disease (% yes (n))	67.0 (892)
Number of metastatic sites including lymph node involvement (mean (SD))	1.24 (1.23)
Number of metastatic sites excluding lymph node involvement (mean (SD))	0.78 (1.05)
Symptom Characteristics at Enrollment	
Lee Fatigue Scale: evening fatigue score (mean (SD))	5.34 (2.14)
Lee Fatigue Scale: morning fatigue score (mean (SD))	3.13 (2.25)
Lee Fatigue Scale: evening energy score (mean (SD))	3.54 (2.04)
Lee Fatigue Scale: morning energy score (mean (SD))	4.40 (2.25)
Center for Epidemiological Studies-Depression Scale score (mean (SD))	12.96 (9.79)
General Sleep Disturbance Scale score (mean (SD))	52.54 (20.23)
Trait Anxiety score (mean (SD))	35.13 (10.41)
State Anxiety score (mean (SD))	33.96 (12.35)
Attentional Function Index score (mean (SD))	6.37 (1.82)
Pain present (% yes (n))	72.8 (969)

Abbreviations: gm/dL = grams per deciliter; kg/m^2 = kilograms per meters squared; SD = standard deviation; RT = radiation therapy.

Changes in Sleep Disturbance Over Time

The first HLM analysis examined how sleep disturbance scores changed within the two cycles of CTX. The estimates for the initial piecewise model are presented in Table 2. The linear and quadratic trends for both the first and second CTX cycles were significant (all $p<.0001$). Since the model was unconditional (i.e., no covariates), the intercept represents the average sleep disturbance score at enrollment (i.e., 52.536 on a scale of 0 to 147). The estimated linear piecewise rates of change were 6.054 ($p<.0001$) and 2.528 ($p<.0001$) for piecewise linear 1 and piecewise linear 2, respectively. The estimated quadratic piecewise rates of change were -3.759 ($p<.0001$) and -0.880 ($p<.0001$) for piecewise quadratic 1 and piecewise quadratic 2,

respectively. The combination of each coefficient determines the curves for the two piecewise components' changes in sleep disturbance scores over time.

Table 2. Hierarchical Linear Model for Sleep Disturbance

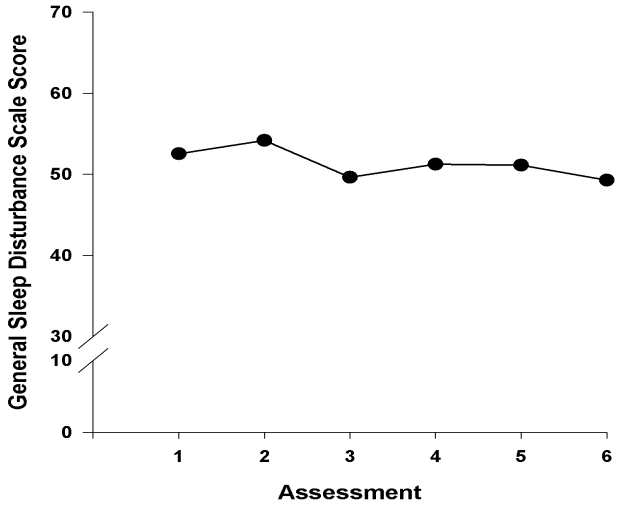
Sleep Disturbance	Coefficient (SE)	
	Unconditional Model	Final Model
Fixed effects		
Intercept	52.536 (.576)$^{+}$	52.543 (.444)$^{+}$
Piecewise 1 – linear rate of change	6.054 (.724)$^{+}$	6.008 (.726)$^{+}$
Piecewise 1 – quadratic rate of change	-3.759 (.348)$^{+}$	-3.732 (.349)$^{+}$
Piecewise 2 – linear rate of change	2.528 (.474)$^{+}$	2.497 (.475)$^{+}$
Piecewise 2 – quadratic rate of change	-0.880 (.153)$^{+}$	-0.871 (.153)$^{+}$
Time invariant covariates		
Intercept		
Body mass index		0.174 (.066)*
Karnofsky Performance Status		-0.155 (.033)$^{+}$
Trait anxiety		0.168 (.059)*
Depressive symptoms		0.308 (.069)$^{+}$
Morning fatigue		2.978 (.270)$^{+}$
Evening fatigue		1.155 (.203)$^{+}$
Attentional function		-1.334 (.330)$^{+}$
Piecewise 1 – linear rate of change		
Education		0.721 (.227)*
Sleep disturbance		0.173 (.044)$^{+}$
Morning fatigue		-1.942 (.442)$^{+}$
Attentional function		1.271 (.506)*
Piecewise 1 – quadratic rate of change		
Education		-0.312 (.108)*
Sleep disturbance		-0.069 (.021)*
Morning fatigue		0.723 (.204)$^{+}$
Attentional function		-0.476 (.233)*
Variance components		
In intercept	18.334^{+}	12.509^{+}
Goodness-of-fit deviance (parameters estimated)	55485.839 (7)**	54613.675 (22)
Model comparison χ^2 (df)		872.164 (15)**

*p<.05, **p<.001, +p<.0001

Figure 1A displays the mean sleep disturbance scores over the two cycles of CTX. Sleep disturbance severity peaked at assessment 2 then decreased at assessment 3, rose slightly at assessment 4, and then decreased at assessments 5 and 6. These results indicate a sample-wide change in sleep disturbance scores over time. However, they do not indicate that all of the patients' sleep disturbance severity scores changed at the same rate over time. The

variance components (Table 2) suggest that considerable inter-individual variability existed in the trajectories of sleep disturbance. A spaghetti plot of a random sample of 50 patients demonstrates the inter-individual variability in sleep disturbance (Figure 1B). These results supported additional analyses of predictors of inter-individual differences in initial levels as well as in the trajectories of sleep disturbance severity scores.

A.



B.

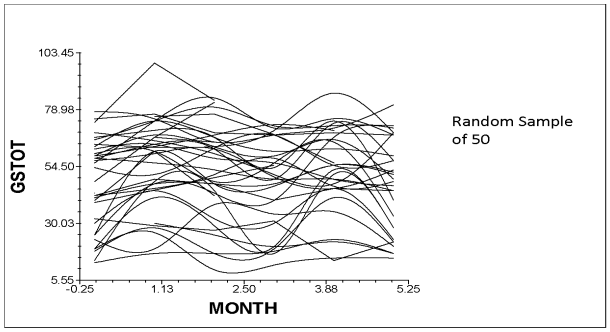


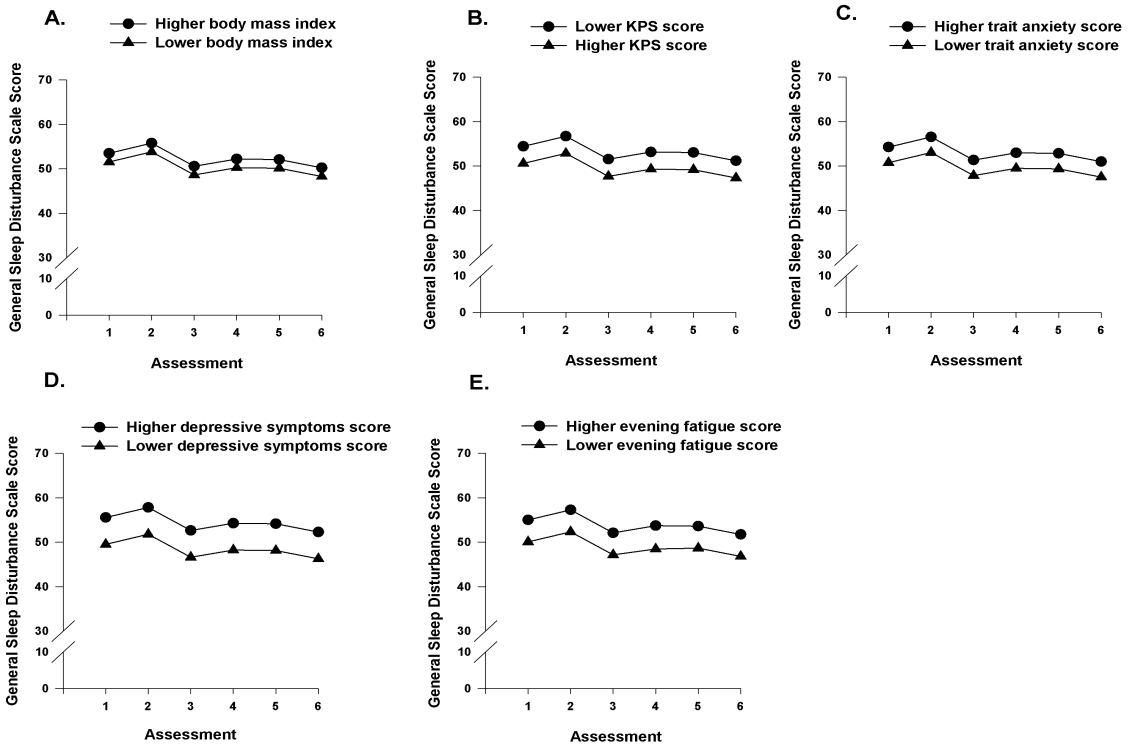
Figure 1 A – Piecewise model of mean sleep disturbance scores for six assessment points over two cycles of chemotherapy (CTX). Figure 1 B - Spaghetti plots of individual sleep disturbance trajectories for a random sample of 50 patients over two cycles of CTX. Abbreviation: GSTOT = General Sleep Disturbance Scale total score.

Characteristics Associated with Initial Levels of Sleep Disturbance

As shown in the final model (Table 2), the two clinical characteristics that predicted inter-individual differences in initial levels of sleep disturbance were BMI and KPS score. The symptom characteristics that predicted inter-individual differences in initial levels of sleep disturbance were trait anxiety, depression, and evening fatigue.

To illustrate the effects of the various intercept predictors, Figures 2 A-E display the adjusted change curves for sleep disturbance that were estimated based on differences in BMI (i.e., one SD above and below the mean BMI score), KPS score (i.e., one SD above and below the mean KPS score), trait anxiety (i.e., one SD above and below the mean STAI-T score), depressive symptoms (i.e., one SD above and below the mean CES-D score), and evening fatigue (i.e., one SD above and below the mean LFS evening fatigue score).

Figures 2 A-E- Influence of enrollment scores for body mass index (A), Karnofsky Performance Status (KPS) score (B), trait anxiety (C), depressive symptoms (D), and evening fatigue (E), on inter-individual differences in the intercept for sleep disturbance.



Characteristics Associated with Trajectories of Sleep Disturbance

As shown in the final model (Table 2), the two characteristics that predicted inter-individual variability in the trajectories of sleep disturbance (i.e., slope) were level of education and sleep disturbance scores at enrollment. Both of these characteristics predicted only the linear and quadratic components of PW1. To illustrate the effects of these two characteristics, Figure 3 A-B display the adjusted change curves for sleep disturbance that were estimated based on differences in level of education (i.e., one SD above and below the mean number of years of education) and sleep disturbance (i.e., one SD above and below the mean GSDS score).

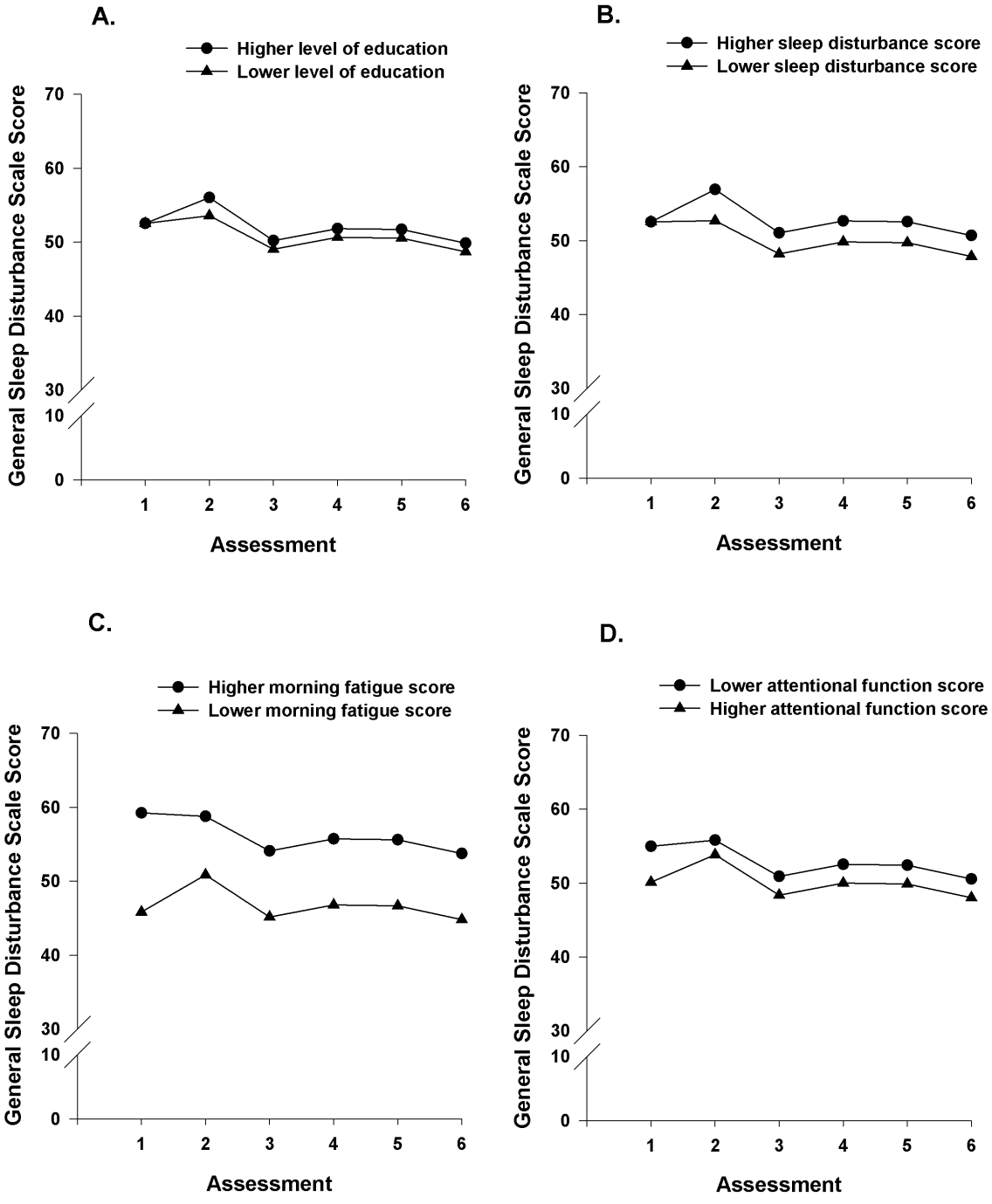
Characteristics Associated with Initial Levels and Trajectories of Sleep Disturbance

As shown in the final model (Table 2), the two characteristics that predicted initial levels as well as the trajectories of sleep disturbance were morning fatigue and attentional function.

Both of these characteristics predicted only the linear and quadratic components of PW1.

Figures 3 C-D display the adjusted change curves for sleep disturbances that were estimated based on differences in morning fatigue (i.e., one SD above and below the mean LFS morning fatigue score) and attentional function (i.e., one SD above and below the mean AFI score).

Figures 3 A-D Influence of enrollment scores for level of education (A) and sleep disturbance (GSDS score) (B), on the slope parameters for sleep disturbance and influence of enrollment scores for morning fatigue (C) and attentional function (D) on inter-individual differences in the intercept and slope parameters for sleep disturbance.


A.
Higher level of education
Lower level of education
General Sleep Disturbance Scale Score
70
60
50
40
30
10
0
1
2
3
4
5
6
Assessment
B.
Higher sleep disturbance score
Lower sleep disturbance score
General Sleep Disturbance Scale Score
Assessment
C.
Higher morning fatigue score
Lower morning fatigue score
General Sleep Disturbance Scale Score
Assessment
D.
Lower attentional function score
Higher attentional function score
General Sleep Disturbance Scale Score
Assessment

Discussion

This study is the first to evaluate for inter-individual differences in the severity of sleep disturbance as well as for characteristics that were associated with these differences in a large sample of oncology outpatients receiving CTX. It is important to note that at enrollment, GSDS scores were above the cut-off for clinically meaningful levels of sleep disturbance. Across two cycles of CTX, a variety of demographic, clinical, and symptom characteristics were associated with inter-individual differences in initial levels (i.e., BMI, KPS, trait anxiety, depression, evening fatigue), trajectories (i.e., education, sleep disturbance), or both initial levels and the trajectories (i.e., morning fatigue, attentional function) of sleep disturbance. For the purposes of this discussion, these characteristics are grouped into non-modifiable (i.e., education, trait anxiety) and modifiable (i.e., BMI, KPS score, depression, morning and evening fatigue, sleep disturbance, attentional function) risk factors for sleep disturbance during CTX.

Non-modifiable Characteristics

Consistent with findings from a previous study of sleep disturbance in women before and after surgery for breast cancer,(49) a higher level of education was associated with a slightly worse trajectory of sleep disturbance. In our relatively well educated sample, this difference may be associated with higher levels of distress associated with increased knowledge of the disease and its treatment.(49)

Because trait anxiety is described as a disposition toward experiencing anxiety,(50) it was classified as a non-modifiable characteristic. Consistent with previous reports that found a positive association between anxiety and sleep disturbance in oncology patients,(51-54) (Remove 52 and 54, add PMCID: PMC3593248) higher levels of trait anxiety at enrollment were associated with higher initial levels of sleep disturbance. Given that the mean STAI-T score for our sample at enrollment was above the clinically meaningful cutoff score, clinicians need to assess for the co-occurrence of trait anxiety and sleep disturbance in oncology patients undergoing CTX.

Modifiable Characteristics

Consistent with a previous study of breast cancer patients at the initiation of radiation therapy (RT),(45, 55) higher BMI was associated with higher initial levels of sleep disturbance. The mean BMI of our study sample was 26.16, which is considered overweight or pre-obese.(56) Obesity has been associated with a higher prevalence of insomnia and restless leg syndrome, which contributes to disturbances throughout the sleep cycle.(57) Additionally, it is estimated that 70% of individuals with obstructive sleep apnea are clinically obese.(57) Weight reduction interventions, along with treatments for obstructive sleep apnea, when clinically indicated, may decrease the severity of sleep disturbance in obese cancer patients receiving CTX.

Consistent with findings from a study of breast cancer patients who were evaluated prior to surgery,(49) lower KPS scores were associated with higher initial levels of sleep disturbance. The average KPS score of this sample was 80, which indicates that these patients were able to carry out normal activities and to work without any special care needed.(7) However, at a KPS score of 68.0 (i.e., 1 SD below the mean), patients indicated that they were unable to work and required occasional assistance for their personal needs at home (7). While the exact relationships between sleep disturbance and decrements in functional status warrant additional investigation, the initiation of interventions to improve functional status early in the course of CTX may have a positive impact on both sleep disturbance and functional status. For example, exercise interventions are known to improve physical functioning in cancer patients undergoing active treatment.(58) The converse may also be true in that improvements in physical functioning may improve sleep. This hypothesis is supported by findings from a study of patients with coronary artery disease, in which a nurse-led sleep intervention not only improved sleep quality, duration, and efficiency, but had a positive impact on patients' functional status.(59)

Consistent with reports of sleep disturbance in men with prostate cancer during and after RT,(47) inpatients with hepatocellular carcinoma,(60) and women undergoing CTX for breast

cancer,(55) depression was associated with higher initial levels of sleep disturbance. While the average CES-D score of 12.96 was below the clinically meaningful cut-off score, patients whose CES-D score was one SD above the mean (i.e., 22.8) were well above the cutoff score of ≥16. In addition, approximately 20% of the patients in our study reported depression as a concurrent medical condition. In the general population, insomnia is common in depressed patients. In addition, sleep disturbance is considered a risk factor for depression.(61) While a positive relationship exists between sleep disturbance and depression, causal associations remain to be determined. Our findings suggest that oncology clinicians need to assess for the co-occurrence of depression and sleep disturbance in patients undergoing CTX. In addition, exercise(58, 62) and cognitive behavioral therapy (63) may be useful interventions for both depression and sleep disturbance.

Consistent with findings that fatigue is highly prevalent during and after cancer treatment (64) and that associations exist between fatigue and sleep disturbance,(55, 65) higher levels of both morning and evening fatigue were associated with both initial levels (i.e., morning and evening fatigue) and trajectories (i.e., morning fatigue) of sleep disturbance. Recent findings suggest that morning and evening fatigue are distinct but related symptoms that warrant separate assessments in oncology patients.(11, 66-68) At the initiation of the current study, both morning and evening fatigue scores approached the clinically meaningful cutoff values. As illustrated in Figure 3C, for those patients whose morning fatigue scores were one SD above the mean (i.e., 5.38), their sleep disturbance score was predicted to be approximately 60. This level of sleep disturbance is reported by shift workers (69) and mothers and fathers caring for a newborn infant.(29) Again, the co-occurrence of these two symptoms warrants ongoing assessments in patients receiving CTX. A number of interventions (e.g., exercise, cognitive-behavioral therapies, yoga, acupuncture) may be useful to decrease fatigue in oncology patients.(58, 62-65). Clinicians can recommend these interventions to decrease fatigue and sleep disturbance during CTX.

Consistent with previous findings in patients with breast cancer, (70-72) lower attentional function scores were associated with higher levels of sleep disturbance in our study. The relationship between sleep disturbance and changes in attentional function may be influenced by other factors that warrant consideration in future studies. While age was not a significant predictor of sleep disturbance in our study, age-related declines in cognitive function were found to have an additive effect on the association between sleep disturbance and decreases in attentional function in women with breast cancer. (72, 73) Another factor that may influence the association between sleep disturbance and attentional function is education. For example, in a study of patients with breast cancer,(72) higher levels of insomnia symptoms were associated with lower levels of attentional function, particularly in women who had a college degree. While a number of interventions have resulted in improvements in attentional function (e.g., administration of antioxidants;(73) development and maintenance of supportive social relationships;(71) medical qigong;(74)) computer based cognitive training;(75) exercise (70, 73)) additional research is needed to confirm the efficacy of these interventions for both decrements in attentional function and sleep disturbance.

Consistent with a previous study(76) and a metasynthesis (6) that described high levels of sleep disturbance in breast cancer patients prior to CTX, the average GSDS score for our sample was 52.54, which is above the clinically meaningful cutoff score of 43. Our study appears to be the first to associate lower levels of sleep disturbance at enrollment with a worse trajectory of sleep disturbance over two cycles of CTX (Figure 3B). However, this effect was relatively modest.

Limitations

Several limitations of our study should be acknowledged. The study population was predominately female, White, college educated, and had metastatic disease, suggesting that the sample may not be representative of the United States oncology population. Because patients were recruited at various time points in their course of CTX, changes in sleep disturbance from

the initiation of CTX cannot be evaluated. While the sample size was very large, which increases the generalizability of the study findings, these patients received a wide variety of CTX regimens. Therefore, differences in sleep disturbance associated with different CTX regimens cannot be evaluated. Finally, future studies need to include objective measures of sleep disturbance.

Conclusions

Despite these limitations, this study is the first to identify modifiable (i.e., BMI, KPS score, depression, morning and evening fatigue, sleep disturbance, attentional function) and non-modifiable (i.e., education, trait anxiety) characteristics associated with sleep disturbance in patients receiving CTX. These characteristics can be used to identify patients at higher risk of sleep disturbance and provide these patients with specific interventions to improve sleep during and after treatment. The current findings should be confirmed in a sample of patients starting at the initiation of CTX and continuing through to the completion of their CTX treatment. Future studies need to investigate the impact of multiple co-occurring symptoms and symptom clusters on the trajectories of sleep disturbance. In addition, research is needed on the efficacy of interventions that address modifiable characteristics associated with sleep disturbance.

Until findings from these additional studies are available, treatments for sleep disturbance include cognitive behavioral interventions, complementary therapies, educational/informational interventions, mindfulness interventions, and exercise (for reviews see (55, 58, 63, 77). Among these interventions, exercise may be the most efficacious because it may have a mediating effect on some of the modifiable characteristics identified in our study, namely high BMI and associated comorbidities, (56) poor functional status,(58) depression, (58, 62) fatigue,(58, 62, 64) and decreased attentional function.(70, 73)

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Appendix 1

Supplementary Table 1. Potential Predictors of Intercept, and Piecewise 1 and Piecewise 2 Linear and Quadratic Components for Sleep Disturbance

Potential Predictors	Intercept	Piecewise 1 Linear Component	Piecewise 1 Quadratic Component	Piecewise 2 Linear Component	Piecewise 2 Quadratic Componen
Demographic Characteristics					
Age	X				X
Sex	X				X
Ethnicity (White versus Non-White)					
Education		X	X		
Marital status	X				
Live alones	X				
Employment status	X				X
Child care responsibilities	X				
Clinical Characteristics					
Body mass index (kg/m^2)	X			X	X
Past or current history of smoking					
Hemoglobin (gm/dL)					
Karnofsky Performance Status Scale score	X			X	X
Self-administered Comorbidity Questionnaire score	X			X	X
Exercise on a regular basis	X				X
Time since cancer diagnosis					
Any prior cancer treatments					
Number prior cancer treatments					
Type of prior cancer treatments					
Presence of metastatic disease	X				
Number of metastatic sites including lymph node involvement	X				X
Number of metastatic sites excluding lymph node involvement					X

Potential Predictors	Intercept	Piecewise 1 Linear Component	Piecewise 1 Quadratic Component	Piecewise 2 Linear Component	Piecewise 2 Quadratic Componen
Symptom Characteristics					
Lee Fatigue Scale: Evening fatigue score at enrollment	X			X	X
Lee Fatigue Scale: Morning fatigue score at enrollment	X	X	X	X	X
Lee Fatigue Scale: Evening energy score at enrollment	X				X
Lee Fatigue Scale: Morning energy score at enrollment	X	X	X	X	X
Center for Epidemiological Studies-Depression Scale score at enrollment	X			X	X
General Sleep Disturbance Scale score at enrollment		X	X	X	X
Trait Anxiety score at enrollment	X			X	X
State Anxiety score at enrollment	X			X	X
Attentional Function Index score at enrollment	X	X	X	X	X
Pain present at enrollment	X			X	X

u= From exploratory analysis had a *t*-value of ≥2.0.

Abbreviations: gm/dL = grams per deciliter; kg/m^2 = kilogram per meters squared.

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