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Neuropsychological Symptoms and Intrusive Thoughts Are Associated With Worse Trajectories of Chemotherapy-Induced Nausea

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Abstract

Background: While chemotherapy-induced vomiting is well-controlled with evidenced-based anti-emetic regimens, chemotherapy-induced nausea (CIN) remains a significant clinical problem.

Objectives: Study purposes, in a sample of outpatients with breast, gastrointestinal (GI), gynecological (GYN), or lung cancer who received two cycles of chemotherapy (CTX, n=1251), were to evaluate for inter-individual differences in the severity of CIN and to determine which demographic, clinical, symptom, and stress characteristics are associated with higher initial levels as well as with the trajectories of CIN.

Methods: Patients were recruited during their first or second cycle of CTX. Patients completed self-report questionnaires a total of six times over two cycles of CTX. Hierarchical linear modeling was used to evaluate for inter-individual differences in and characteristics associated with the severity of CIN.

Results: Across the two cycles of CTX, higher levels of sleep disturbance, depression, and morning fatigue, as well as higher levels of intrusive thoughts were associated with higher initial levels of CIN. In addition, lower functional status scores and shorter cycle lengths were associated

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with higher initial levels of CIN and younger age and higher emetogenicity of the CTX regimen were associated with both higher initial levels as well as worse trajectories of CIN severity.

Conclusions: These findings suggest that common symptoms associated with cancer and its treatment are associated with increased severity of CIN. Targeted interventions for these symptoms may reduce the burden of unrelieved CIN.

INTRODUCTION

While the occurrence and severity of chemotherapy-induced vomiting (CIV) has decreased with anti-emetic prophylaxis, unrelieved chemotherapy-induced nausea (CIN), that affects 30% to 60% of oncology patients, remains a significant clinical problem.[1,2] One of the major challenges with determining specific risk factors for the occurrence and/or severity of CIN is that CIN was not assessed as a unique symptom but rather as a composite symptom that included vomiting (i.e., chemotherapy-induced nausea and vomiting (CINV)).[3]

In the two studies that investigated risk factors for the occurrence[2] and severity[4] of CIN, demographic and clinical characteristics were the foci of these investigations. Across these cross-sectional[2] and longitudinal[4] studies, risk factors for CIN included: younger age,[4] lower level of education,[2] having childcare responsibilities,[2,4] poorer functional status,[2,4] a higher number of co-morbidities,[2] increased emetogenicity of the chemotherapy (CTX) regimen,[4] shorter CTX cycle length,[2] and an inadequate antiemetic regimen.[2] While most of these risk factors are not modifiable, they can be used to identify patients at increased risk for CIN. An identification of modifiable risk factors for CIN may allow for the development and testing of novel interventions to decrease this debilitating side effect of CTX.

Emerging evidence suggests that the microbiome-gut-brain-axis (MGBA) plays a role in the development of a number of “neuropsychological” symptoms associated with the administration of CTX[5–7] and reactions to stress.[8,9] In addition to its direct inflammatory effects on the gastrointestinal (GI) tract[10,11] and associated increase in GI symptoms,[4,12] CTX alters the functioning of the gut microbiome which regulates epithelial permeability and host immunity[5,7] and modulates a number of brain functions.[13] These CTX-induced changes alter the bidirectional communications between the gut microbiome and the brain that are mediated by vagal activation and the serotonergic system. These bidirectional changes in communication within the MGBA are implicated in the development of chronic pain[6] as well as in changes in mood and cognition.[9] In addition, alterations in the gut microbiome affect the functioning of the hypothalamic-pituitary-adrenal (HPA) axis which can influence sleep quality, anxiety, depression, and reactions to stress.[9,14]

While most of the research on symptoms associated with alterations in the MGBA is preclinical (for reviews see 5–7, 9, 13) or done in patients with other chronic medical conditions,[15] evidence from our research group suggests that compared to patients who do not report the occurrence of CIN, patients with CIN have changes in gene expression associated with perturbations in pathways involved in the MGBA.[12] In addition, we found that in the same sample of patients, over two cycles of CTX, higher CIN severity scores were associated with higher levels of a number of GI symptoms (i.e., vomiting, feeling bloated, lack of appetite, difficulty swallowing, mouth sores, and constipation).[4] In this later

paper,[4] we hypothesized that these additional GI symptoms were related to CTX-induced changes in the MGBA.

Given the limited evidence on modifiable risk factors associated with increased levels of CIN; the emerging evidence on associations between CTX-induced changes in MGBA and a number neuropsychological symptoms (i.e., pain, fatigue, sleep disturbance, cognitive changes, depression, anxiety)[5–7,13] and stress;[9] and our own preliminary data;[2,4,12] in this study, we extend our previous findings to examine the relationships among a number of neuropsychological symptoms, as well as stress measures and CIN severity. Specifically, the purposes of this study, in a sample of outpatients with breast, gastrointestinal (GI), gynecological (GYN), or lung cancer who received two cycles of CTX (n=1251), were to evaluate for inter-individual differences in the severity of CIN and to determine which demographic, clinical, symptom, and stress characteristics are associated with higher initial levels as well as with the trajectories of CIN.

METHODS

Patients and Settings

This analysis is part of a larger, longitudinal study, of the symptom experience of oncology outpatients receiving CTX whose details are published elsewhere.[2,4,16,17] 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.

Study Procedures

The study was approved by the Institutional Review Board at each of the study sites. Of the 2234 patients approached, 1343 consented to participate (60.1% response rate). The major reason for refusal was being overwhelmed with their cancer treatment. From February 2010 to May 2015, eligible patients were approached in the infusion unit during their first or second cycle of CTX by a member of the research team to discuss study participation and obtain written informed consent. Patients completed study questionnaires in their homes, a total of six times over two cycles of CTX. Medical records were reviewed for disease and treatment information.

Instruments and Coding of Drug Regimens

Demographic and clinical characteristics -—Patients completed a demographic questionnaire, the Karnofsky Performance Status (KPS) scale,[18] and the Self-Administered Comorbidity Questionnaire (SCQ).[19] Medical records were reviewed for disease and treatment information.

Assessment of nausea severity -—Quality of Life-Patient Version (QOL-PV) scale is a 41-item instrument. One item on QOL-PV asked patients to rate the severity of their

nausea using a 0 (no problem) to 10 (severe problem) numeric rating scale (NRS). The QOL-PV has well established validity and reliability.[20,21]

Assessment of symptoms -—Instruments used to evaluate symptoms in this study were described previously.[2] Lee Fatigue Scale (LFS) was used to assess diurnal variations in fatigue and decrements in energy.[22] Center for Epidemiological Studies-Depression scale (CES-D) assessed depressive symptoms.[23] General Sleep Disturbance Scale (GSDS) evaluated sleep quality.[24] Spielberger State-Trait Anxiety Inventories (STAI) evaluated state and trait anxiety.[25] Attentional Function Index (AFI) assessed difficulties with attention and executive function.[26] Brief Pain Inventory evaluated occurrence of pain.[27]

Assessment of stress -—Perceived Stress Scale (PSS) measured general stress as a result of life circumstances.[28] Impact of Event Scale-Revised (IES-R) measured stress associated with the cancer and its treatment. IES-R has three subscales that evaluate levels of intrusion, avoidance, and hyperarousal.[29]

Coding of the emetogenicity of the CTX regimens -—Using the Multinational Association for Supportive Care in Cancer (MASCC) guidelines,[30] each CTX drug in the regimen was classified as having: minimal, low, moderate, or high emetogenic potential. The emetogenicity of the regimen was categorized into one of three groups (i.e., low/minimal, moderate, high) based on the CTX drug with highest emetogenic potential.

Coding of the antiemetic regimens -—Each antiemetic was coded as either a neurokinin-1 (NK-1) receptor antagonist, a serotonin receptor antagonist, a dopamine receptor antagonist, prochlorperazine, lorazepam, or a steroid. The antiemetic regimens were coded into one of four groups: none (i.e., no antiemetics administered); steroid alone or serotonin receptor antagonist alone; serotonin receptor antagonist and steroid; or NK-1 receptor antagonist and two other antiemetics (e.g., a serotonin receptor antagonist, dopamine receptor antagonist, prochlorperazine, lorazepam and/or a steroid).

Data Analyses

Descriptive statistics and frequency distributions were generated for the sample characteristics, as well as for the severity of each of the symptoms and stress measures at enrollment using the Statistical Package for the Social Sciences (SPSS) version 25.[31] Hierarchical linear modeling (HLM), based on full maximum likelihood estimation, was used to evaluate for inter-individual variability in initial levels and trajectories of CIN severity.[32] The HLM methods are described in detail elsewhere.[4] First, intra-individual variability in CIN severity over time was examined. A piecewise model strategy was employed to evaluate the pattern of change in nausea over time because the six assessments encompassed two cycles of CTX. The six assessments were coded into two pieces. Assessments 1 (the week prior to the second or third cycle of CTX), 2 (the week after the administration of CTX), and 3 (two weeks after the administration of CTX) comprised the first piece (PW1) that was used to model changes over time 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.

Second, inter-individual differences in the piecewise trajectories of CIN were examined by modeling the individual change parameters (i.e., intercept and slope parameters) as a function of proposed predictors at level 2. Table 1 lists the potential predictors for CIN that were evaluated based on a review of literature.[2,33–35]

To improve estimation efficiency and to 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. All potential significant predictors from the exploratory analyses were entered into the model to predict each individual change parameter. Demographic characteristics were entered first in a backward stepwise approach, in which the potential predictor variables that were not statistically significant were deleted from the model one by one. Next, clinical characteristics, followed by symptom and stress variables, were entered into the model using the same backward stepwise approach. Only predictors that maintained a statistically significant contribution (*p*-value of <.05) in conjunction with other predictors were retained in the final model.

RESULTS

Sample Characteristics

Demographic, clinical, symptom, and stress characteristics of the sample (n=1251) are summarized in Table 2. The sample was predominately female (78.0%) with a mean age of 57.00 (±12.23) years. Patients had an average of 16.23 (±3.00) years of education, a body mass index of 26.24 (±5.69), and a KPS score of 80.14 (±12.33). Patients were 1.96 (±3.84) years from their cancer diagnosis (median = 0.42) and had an average of one metastatic site. Patients were primarily being treated with 21-day CTX cycles (50.4%), moderately emetogenic CTX (60.6%), and an antiemetic regimen that included a serotonin receptor antagonist and a steroid (46.5%).

The mean morning energy LFS score was below the clinically meaningful cutoff (i.e., ≤6.2). The mean scores on the GSDS, as well as on the STAI-T and STAI-S scales, were above the clinically meaningful cutoffs for sleep disturbance (i.e., ≥43), trait anxiety (i.e., ≥31.8), and state anxiety (i.e., ≥32.2), respectively. The mean total IES-R score did not exceed the clinically meaningful cutoff score of ≥33.

Changes in CIN Severity Over Time

The first HLM analysis examined how CIN severity changed within the two cycles of CTX. The estimates for the initial piecewise model are presented in Table 3. As described previously,[4] the linear and quadratic trends for both cycles of CTX were significant (all p<.0001). Since the model was unconditional, the intercept represents the average CIN severity score at enrollment (i.e., 2.697 on a 0 to 10 NRS). Estimated linear rates of change in CIN severity were 0.685 and 0.910 (both *p*<.0001) for PW1 and PW2, respectively. Estimated quadratic rates of change in CIN severity were −0.489 and −0.312 (both *p*<.0001) for PW1

and PW2, respectively. The combination of each coefficient determines the curves for the two PW components' changes in CIN severity over time.

Figure 1A displays the estimated CIN severity scores over the two cycles of CTX. Overall, CIN severity peaked at assessment 2, decreased at assessment 3, rose slightly at assessment 4, and then decreased over assessments 5 and 6. These results indicate a sample-wide change in CIN severity over time.[4] However, they do not indicate that all of the patients' CIN severity scores changed at the same rate over time. The variance components (Table 3) suggest that considerable inter-individual variability existed in the trajectories of CIN. These results supported additional analyses of predictors of inter-individual differences in initial levels as well as in the trajectories of CIN severity.

Demographic and Clinical Characteristics Associated with CIN Severity

Age predicted inter-individual differences in both initial levels of CIN as well as in the linear and quadratic components of PW2 (Table 3). Figure 1B displays the adjusted change curves for CIN that were estimated based on differences in age (i.e., younger/older calculated as one standard deviation (SD) above and below the mean age).

The three clinical characteristics that were associated with inter-individual differences in initial levels of CIN were KPS score, cycle length, and emetogenicity of the CTX regimen (Table 3). To illustrate the effects of KPS scores and cycle length, Figures 1C and 1D display the adjusted change curves for CIN that were estimated based on differences in KPS scores (i.e., lower/higher calculated as one SD above and below the mean score) and cycle length (i.e., 14-day cycle, 21-day cycle and 28-day cycle). In addition to predicting initial levels of CIN, emetogenicity of the CTX regimen predicted inter-individual differences in the trajectories of CIN (Figure 1E).

Symptoms and Stress Associated with CIN Severity

As shown in the final model (Table 3), four symptom scores (i.e., depression, sleep disturbance, trait anxiety, morning fatigue) and the intrusion subscale score of the IES-R were associated with inter-individual differences in initial levels of CIN. To illustrate the effects of the various symptoms, Figures 2A–D display the adjusted change curves for CIN severity that were estimated based on differences in symptom scores (i.e., lower/higher calculated as one standard deviation (SD) above and below the mean score for each symptom). Figure 2E displays the adjusted change curves for CIN that was estimated based on differences in IES-R intrusion subscale score (i.e., lower/higher calculated as one SD above and below the mean score). As shown in Figure 3F, morning energy was the only symptom that predicted inter-individual variability in the linear and quadratic components of PW2.

DISCUSSION

As an extension of our previous study to identify modifiable risk factors for increases in CIN severity,[4] this study is the first to identify associations among multiple neuropsychological symptoms, as well as cancer-specific intrusive thoughts, and worse CIN trajectories. In brief, higher levels of sleep disturbance, depression, and morning fatigue, lower levels of trait

anxiety, as well as higher levels of intrusive thoughts were associated with higher initial levels of CIN. Morning energy was the only symptom that influenced the trajectory of CIN. In addition, lower KPS scores and shorter CTX cycle lengths were associated with higher initial levels of CIN and younger age and higher emetogenicity of the CTX regimen were associated with both higher initial levels as well as a worse trajectories of CIN severity.

In our exploratory analyses (Table 1), all of the neuropsychological symptoms that we assessed (i.e., evening fatigue, morning fatigue, evening energy, morning energy, depression, sleep disturbance, trait anxiety, state anxiety, attentional function, pain) were associated with either initial levels and/or the trajectories of CIN severity. However, only five of these symptoms (i.e., sleep disturbance, depression, trait anxiety, morning fatigue, morning energy) remained significant in the final model.

Consistent with previous reports, higher levels of sleep disturbance[2,36–38] and depression[2,38] were associated with increases in CIN severity. Associations among these three symptoms may be partially explained by shared underlying mechanisms. For example, all three symptoms can occur as a result of CTX-induced alterations in the gut microbiome,[12,39–41] as well as through increases in systemic levels of pro-inflammatory cytokines.[42,43] In addition, as was found in previous studies,[36,38,44] higher average fatigue scores were associated with increases in both CIN occurrence rates and severity scores. While in our previous cross-sectional study,[2] patients with CIN reported higher severity scores for both morning and evening fatigue, in the current study, only higher levels of morning fatigue were associated with increases in CIN severity. It is interesting to note that in the HLM model, the symptoms of sleep disturbance, depression, and morning fatigue made independent contributions to explain inter-individual variability in CIN severity. While we[45–48] and others[49,40] have evaluated the impact of the symptom cluster of fatigue, sleep disturbance, depression and/or pain on various QOL outcomes, the underlying hypothesis for this symptom cluster was that cancer and its treatments contributed to cytokine-induced sickness behavior.[51,52] The current findings, as well as our previous reports,[4,12] and the work of others[5–7] suggest that CTX-induced alterations in the MGBA may contribute to the development of these often co-occurring symptoms.

While the symptoms of fatigue and lack of energy have been used interchangeably, work from our group[53,54] and others[55–58] has demonstrated that they are distinct but related symptoms. Of note, in our previous cross-sectional study,[2] patients with CIN reported lower levels of both morning and evening energy. However, in the current study only lower morning energy scores were associated with a worst trajectory of CIN severity during the second cycle of CTX. This association may be linked to the relatively high levels of sleep disturbance reported by this sample.[59,60] This hypothesis warrants confirmation in future studies.

Previous research[61] and our cross-sectional study[2] found that compared to patients without CIN, those with CIN reported higher trait anxiety scores. However, in the current study a lower level of trait anxiety was associated with an increase in CIN severity. One plausible explanation for this discrepancy is that anxious patients in this study may have been receiving anti-anxiety medications. Future studies need to evaluate for cross level

interactions between co-occurring symptoms and pharmacologic and nonpharmacologic interventions and changes in the severity of CIN.

A growing body of evidence suggests that unrelieved stress is associated with disruptions in the MGBA (for reviews see 62–66). While in cancer patients, fear of disease recurrence and/or progression is associated with increased stress,[67] our previous[2] and current study were the first to demonstrate an association between a disease-specific measure of stress (i.e., intrusion subscale of the IES-R) and the occurrence and severity of CIN, respectively. In the multivariate analysis from our previous study, for each one-point increase in the intrusion subscale score, there was a 1.35 increased odds of reporting the occurrence of CIN. In the current study, higher intrusion scores were associated with a higher severity of CIN. This subscale of the IES-R assesses disturbing visuals and feelings associated with the patients' cancer and its treatments.

In our previous longitudinal study, that evaluated associations between a number of GI symptoms and CIN severity,[4] we provided a detailed discussion of the demographic (i.e., younger age, having child care responsibilities) and clinical (i.e., lower KPS score, higher SCQ score, higher emetogenicity of the CTX regimen) characteristics that were included in the final HLM model. In the current study, only three of these characteristics were retained in the final HLM (i.e., age, KPS score, emetogenicity of the CTX regimen) and a new clinical characteristic was identified (i.e., shorter cycle length). Of note and consistent with the current study, in our previous cross-sectional study,[2] compared to patients who received CTX on a 14-day cycle, patients on a 21-day cycle had a 42% decrease in odds of belonging to the CIN group (i.e., CIN occurrence). These findings support the idea that a shorter duration between CTX infusions is associated with increases in both the occurrence and severity of CIN.[68]

Several limitations need to be considered. While this study included a large sample of patients who were assessed six times over two cycles of CTX and evaluated for multiple co-occurring symptoms in the same patients, future studies should enroll patients prior to the initiation of CTX and follow them through to the completion of CTX. In addition, future studies should code not only the emetogenicity of the CTX regimen and the types of anti-emetics presecribed but include an evaluation of whether or not the anti-emetic regimen reflected evidenced-based guideline recommendations. Equally important, the relationships between CIN and other GI symptoms are undoubtedly complex, additional research is warranted using analytic techniques like parallel process growth modeling to determine if a particular GI symptom is influencing the severity of one or more GI symptoms including CIN. Finally, future studies need to collect samples to evaluate for associations between/among changes in the severity of these co-occurring symptoms and changes in the oral and gut microbiota.

Despite these limitations, the findings from this study suggest that common symptoms associated with cancer and its treatment are associated with increased severity of CIN. This work, as well as our previous findings,[2,4,12] provide information on risk factors for CIN occurrence and severity that clinicians can assess and manage. In addition, this work

provides direction for future studies that can directly examine the associations among multiple co-occurring symptoms and CTX-induced alterations in the MGBA.

Disclosures:

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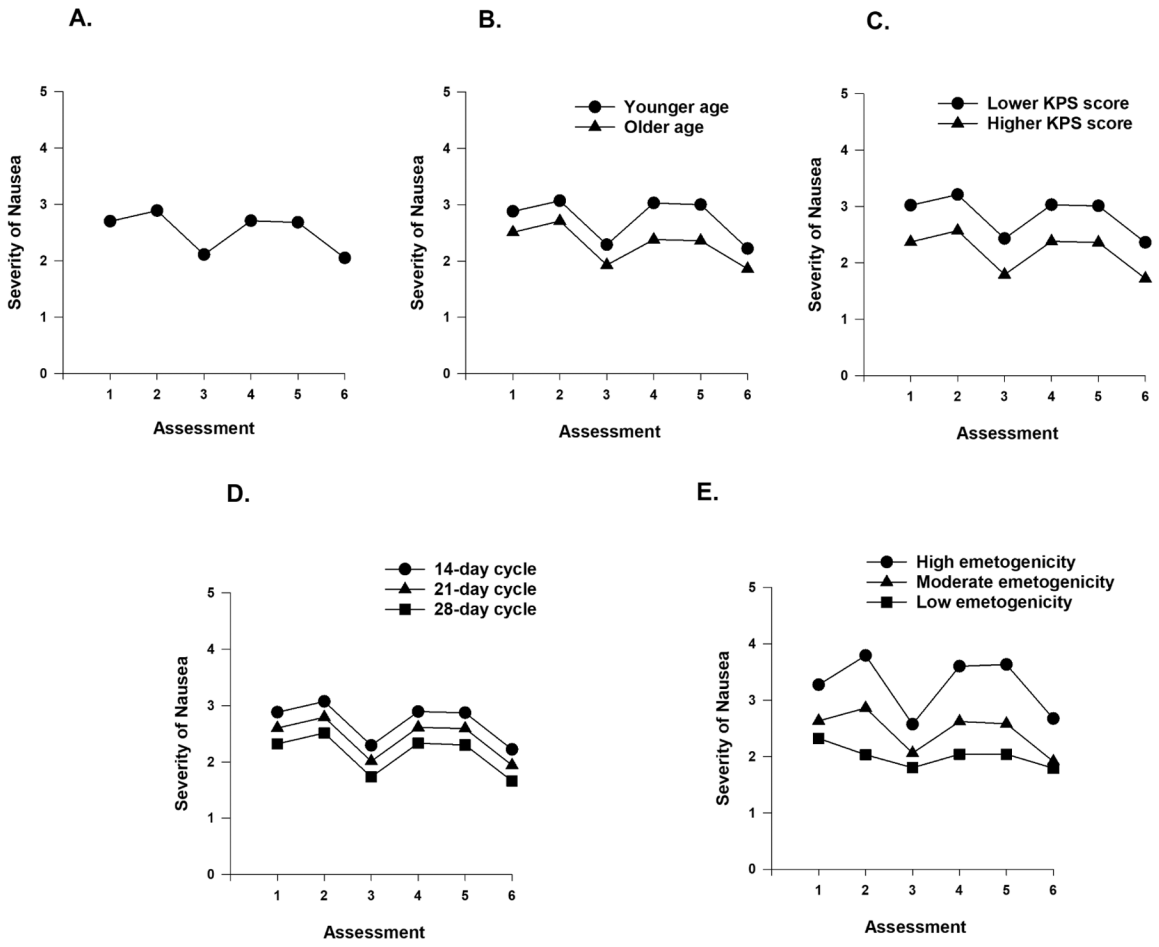

Figure 1.

A-E - Piecewise model of mean nausea severity scores for six assessments over two cycles of chemotherapy (A). Influence of age (B) on inter-individual differences in the intercept and slope parameters for nausea severity. Influence of Karnofsky Performance Status (KPS) score (C) and cycle length (D) on inter-individual differences in the intercept for nausea severity. Influence of emetogenicity of the chemotherapy regimen (E) on inter-individual differences in the intercept and slope parameters for nausea severity.

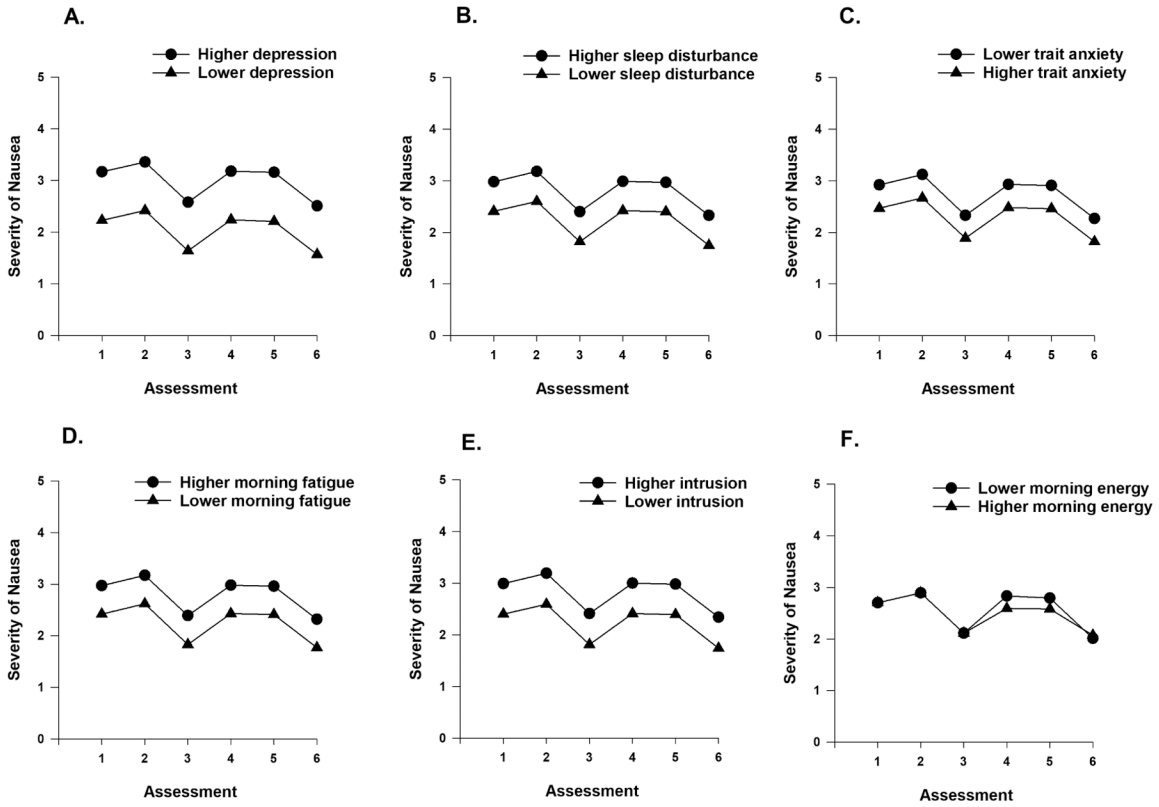

Figure 2.

A-F Influence of depression (A), sleep disturbance (B), trait anxiety (C), morning fatigue (D), and intrusion (E) scores on inter-individual differences in the intercept for nausea severity. Influence of morning energy scores (F) on inter-individual differences in the slope parameters for nausea severity.

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Table 1:

Potential Predictors of the Intercept and Piecewise 1 and Piecewise 2 Linear and Quadratic Components for Nausea

Potential Predictors	Intercept	Piecewise 1 Linear Component	Piecewise 1 Quadratic Component	Piecewise 2 Linear Component	Piecewise 2 Quadratic Component
Demographic Characteristics					
Age	◆	◆	◆	◆	◆
Female	◆			◆	◆
Lives alone					
Married/partnered	◆				
Education	◆				
Employment status					
Child care responsibilities	◆	◆	◆		
Non-White ethnicity	◆			◆	◆
Black vs White					
Asian or Pacific Islander vs White					
Hispanic, Mixed, or Other vs White	◆	◆	◆	◆	◆
Clinical Characteristics					
Body mass index (kg/m^2)					
Past or current history of smoking					
Karnofsky Performance Status Scale score	◆	◆	◆	◆	◆
Number of comorbidities	◆				
Self-administered Comorbidity Questionnaire score	◆	◆	◆		
Exercise on a regular basis					
Time since cancer diagnosis	◆				◆
Any prior cancer treatments					
Number of prior cancer treatments	◆		◆	◆	◆
Presence of metastatic disease	◆		◆	◆	◆
Number of metastatic sites including lymph node involvement	◆	◆	◆		
Cancer diagnosis					
Gastrointestinal vs breast cancer					

Potential Predictors	Intercept	Piecewise 1 Linear Component	Piecewise 1 Quadratic Component	Piecewise 2 Linear Component	Piecewise 2 Quadratic Component
Gynecological vs breast cancer					
Lung vs breast cancer					
Breast vs gastrointestinal				◆	◆
Gynecological vs gastrointestinal					
Lung vs gastrointestinal					
Cycle length	◆	◆	◆		◆
21 day cycle vs 14 day cycle	◆				
28 day cycle vs 14 day cycle	◆	◆	◆	◆	◆
Emetogenicity of chemotherapy regimen					
Moderate vs minimal and Low					
High vs minimal and low	◆	◆	◆	◆	◆
Anti-emetic regimen					
Single antiemetic vs none	◆	◆	◆	◆	◆
Serotonin and steroid vs none					
NK-1 combination vs none	◆	◆	◆	◆	◆
Anti-anxiolytic vs none					
Symptom Characteristics at enrollment					
Lee Fatigue Scale: Evening fatigue score	◆	◆	◆	◆	◆
Lee Fatigue Scale: Morning fatigue score	◆	◆	◆	◆	◆
Lee Fatigue Scale: Evening energy score	◆	◆	◆	◆	◆
Lee Fatigue Scale: Morning energy score	◆		◆	◆	◆
Center for Epidemiological Studies-Depression Scale score	◆	◆	◆	◆	◆
General Sleep Disturbance Scale score	◆	◆	◆	◆	◆
Trait Anxiety score	◆	◆	◆	◆	◆
State Anxiety score	◆	◆	◆	◆	◆
Attentional Function Index score	◆	◆	◆	◆	◆
Occurrence of pain	◆		◆	◆	◆
Stress measures					
Perceived Stress Scale score	◆	◆	◆	◆	◆

Potential Predictors	Intercept	Piecewise 1 Linear Component	Piecewise 1 Quadratic Component	Piecewise 2 Linear Component	Piecewise 2 Quadratic Component
Impact of Event Scale-Revised - Avoidance subscale score	◆	◆	◆	◆	◆
Impact of Event Scale-Revised - Intrusion subscale score	◆	◆	◆	◆	◆
Impact of Event Scale-Revised - Hyperarousal subscale score	◆	◆	◆	◆	◆
Impact of Event Scale-Revised - Total score	◆	◆	◆	◆	◆

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

Abbreviations: kg/m^2 = kilogram per meter squared; NK-1 = Neurokinin-1; vs = versus

Table 2:

Demographic, Clinical, and Symptom Characteristics of the Patients (n=1251)

Demographic Characteristics	
Age (years; mean (SD))	57.00 (12.23)
Gender (% female (n))	78.0 (976)
Ethnicity (% (n))	
White	70.1 (866)
Black	7.2 (89)
Asian/Pacific Islander	12.2 (151)
Hispanic/Mixed/Other	10.5 (130)
Education (years; mean (SD))	16.23 (3.00)
Married or partnered (% yes (n))	64.5 (795)
Lives alone (% yes (n))	21.7 (268)
Currently employed (% yes (n))	35.6 (441)
Child care responsibilities (% yes (n))	22.1 (271)
Income (% yes (n))	
Less than $30,000	17.7 (199)
$30,000 to <$70,000	21.4 (240)
$70,000 to < $100,000	16.8 (189)
More than $100,000	44.0 (494)
Clinical Characteristics	
Number of comorbidities (mean (SD))	2.39 (1.43)
Self-administered Comorbidity Questionnaire score (mean (SD))	5.46 (3.22)
Body mass index (kg/m^2; mean (SD))	26.24 (5.69)
Karnofsky Performance Status score (mean (SD))	80.14 (12.33)
Have you ever considered yourself a smoker (% yes (n))	34.7 (427)
Exercise on a regular basis (% yes (n))	71.0 (868)
Cancer diagnosis (% yes (n))	
Breast	40.2 (503)
Gastrointestinal	30.7 (384)
Gynecological	17.8 (223)
Lung	11.3 (141)
Time since cancer diagnosis (years; mean (SD))	1.96 (3.84)
Time since cancer diagnosis (years; median)	0.42
Any prior cancer treatments (% yes (n))	75.2 (935)
Number prior cancer treatments (mean (SD))	1.59 (1.50)
Chemotherapy cycle length (% (n))	
14 days	42.2 (528)
21 days	50.4 (631)
28 days	7.3 (91)
Emetogenicity of CTX regimen (% (n))	
Minimal/Low	19.6 (245)

Moderate	60.6 (758)
High	19.8 (248)
Antiemetic regimen (% (n))	
None	6.9 (86)
Steroid alone or serotonin receptor antagonist alone	20.1 (252)
Serotonin receptor antagonist and steroid	46.5 (582)
NK-1 receptor antagonist and two other antiemetics	24.1 (301)
Presence of metastatic disease (% yes (n))	67.7 (841)
Number of metastatic sites including lymph node involvement (mean (SD))	1.25 (1.23)
Number of metastatic sites excluding lymph node involvement (mean (SD))	0.79 (1.05)
Symptom Characteristics at Enrollment * (mean (SD))	
Lee Fatigue Scale: Evening fatigue score (>5.6)	5.33 (2.13)
Lee Fatigue Scale: Morning fatigue score (>3.2)	3.11 (2.24)
Lee Fatigue Scale: Evening energy score (<3.2)	3.55 (2.03)
Lee Fatigue Scale: Morning energy score (<6.2)	4.43 (2.23)
Center for Epidemiological Studies-Depression Scale score (>16.0)	12.78 (9.71)
General Sleep Disturbance Scale score (>43.0)	52.41 (20.18)
Trait Anxiety score (>32.2)	35.10 (10.48)
State Anxiety score (>31.8)	33.74 (12.28)
Attentional Function Index score (<5 Low, 5–7.5 Moderate, >7.5 High)	6.41 (1.80)
Occurrence of pain (% (n))	72.0 (893)
Stress Measures at Enrollment (mean (SD))	
Perceived Stress Scale score	18.43 (8.16)
Impact of Event Scale-Revised - Avoidance subscale score	0.95 (0.68)
Impact of Event Scale-Revised - Intrusion subscale score	0.90 (0.70)
Impact of Event Scale-Revised - Hyperarousal subscale score	0.65 (0.66)
Impact of Event Scale-Revised - total score	18.68 (13.05)

Abbreviations: CTX = chemotherapy; kg/m^2 = kilograms per meters squared; NK-1 = neurokinin-1; SD = standard deviation

* Clinically meaningful cutoff scores are in parenthesis after each measure

Table 3.

Hierarchical Linear Model for the Severity of Chemotherapy-Induced Nausea

	Coefficient (SE)	
Nausea	**Unconditional Model**	**Final Model**
Fixed effects		
Intercept	2.697 (.083)+	2.697 (.073)+
Piecewise 1 - linear rate of change	0.685 (.117)+	0.680 (.116)+
Piecewise 1 - quadratic rate of change	−0.489 (.055)+	−0.487 (.054)+
Piecewise 2 - linear rate of change	0.910 (.081)+	0.907 (.080)+
Piecewise 2 - quadratic rate of change	−0.312 (.026)+	−0.310 (.025)+
Time invariant covariates		
Intercept		
Age		−0.015 (.006)*
Karnofsky Performance Status score		−0.026 (.006)+
Trait Anxiety score		−0.021 (.010)*
CES-D Scale score		0.049 (.012)+
GSDS score		0.014 (.004)*
LFS: Morning fatigue score		0.123 (.039)*
IES-R Intrusion Subscale score		0.406 (.112)+
CTX cycle length		−0.282 (.106)*
CTX emetogenicity		
Moderately vs minimal/low emetogenic CTX		0.315 (.192)
Highly vs minimal/low emetogenic CTX		0.950 (.242)+
Piecewise 1 - linear rate of change		
CTX emetogenicity		
Moderately vs minimal/low emetogenic CTX		1.064 (.303)+
Highly vs minimal/low emetogenic CTX		1.696 (.372)+
Piecewise 1 - quadratic rate of change		
CTX emetogenicity		
Moderately vs minimal/low emetogenic CTX		−0.546 (.142)+
Highly vs minimal/low emetogenic CTX		−0.891 (.174)+
Piecewise 2 - linear rate of change		
Age		−0.017 (.006)*
LFS: Morning energy score		−0.082 (.029)*
CTX emetogenicity		
Moderately vs minimal/low emetogenic CTX		0.516 (.209)*

	Coefficient (SE)	
Nausea	**Unconditional Model**	**Final Model**
Highly vs minimal/low emetogenic CTX		1.156 (.257)+
Piecewise 2 - quadratic rate of change		
Age		0.006 (.002)*
LFS: Morning energy score		0.029 (.010)*
CTX emetogenicity		
Moderately vs minimal/low emetogenic CTX		−0.187 (.067)*
Highly vs minimal/low emetogenic CTX		−0.374 (.082)+
Variance components		
Intercept	6.466+	4.512+
Piecewise 1 - linear rate of change - slope	2.726+	2.349+
Piecewise 1 - quadratic rate of change - slope	0.460*	0.353*
Piecewise 2 - linear rate of change - slope	1.907+	1.587+
Piecewise 2 - quadratic rate of change - slope	0.182+	0.149+
Goodness-of-fit deviance (parameters estimated)	28588.996 (21)**	28176.626 (43)
Model comparison x^2 (df)		412.370 (22)**

*p<.05,

**p<.001,

+p<.0001

Abbreviations: CES-D = Center for Epidemiological Studies-Depression; CTX = chemotherapy; df = degrees of freedom; GSDS = General Sleep Disturbance Scale; IES-R = Impact of Event Scale-Revised; LFS = Lee Fatigue Scale; SE = standard error