Symptom trajectories during chemotherapy in outpatients with lung cancer colorectal cancer, or lymphoma.

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Abstract:

Purpose

Pain, depression, distress, fatigue, and sleep disturbance are common symptoms in oncology patients, but little data are available that examine the trajectories of these symptoms during chemotherapy (CTX). The purposes of this study were to examine the trajectories of these symptoms during the first six cycles of CTX and to determine whether individual characteristics predicted the trajectories of these symptoms.

Methods

Oncology outpatients (n = 118) with newly diagnosed lung cancer, colorectal cancer, or lymphoma rated symptoms using an electronic patient care monitor system. Pain, fatigue, and sleep disturbance were rated on 0–10 numeric rating scales; depression and distress were evaluated using scales converted to normalized T scores. Latent growth curve analyses (LGCA) examined for intra- and inter-individual differences in the trajectories of these five symptoms during the six cycles of CTX.

Results

Symptoms were present at the initiation of CTX ($p < 0.0001$) for all symptoms ($p < 0.05$). Distress ($p = 0.03$) and pain ($p = 0.02$) intensity decreased significantly over the six cycles of CTX. Advanced disease and a higher number of comorbidities predicted higher fatigue at baseline ($p = 0.02$ and 0.01 respectively). A diagnosis of lung cancer predicted an increasing intensity of fatigue during CTX ($p = 0.04$). Concurrent radiation therapy predicted more intense pain over time ($p = 0.03$).

Conclusions

While symptom trajectories were highly variable in patients undergoing initial CTX, the majority of the symptom intensity scores decreased over time. However, patients with lung cancer, those with a higher number of comorbidities, and those with advanced disease experienced more intense fatigue and sleep disturbance over time.

Keywords: chemotherapy | oncology | chemotherapy side effects | lung cancer | colorectal cancer | lymphoma | outpatient chemotherapy treatment

Article:

Introduction

While advances in early detection and treatment of cancer have led to increased survival rates, strides in symptom management have not kept pace (Patrick et al., 2003). Patients continue to experience an array of cancer and treatment-related symptoms that have deleterious effects on quality of life (QOL). Pain, depression, and fatigue are three of the most common symptoms associated with cancer and its treatment (Patrick et al., 2003). Sleep disturbances are prevalent and often coexist with pain, depression, and fatigue (Berger et al., 2005). In addition, distress, defined as the unpleasant experience of coping with cancer and its physical symptoms (NCCN., 1999 and Redeker et al., 2000), can co-occur with these symptoms. These symptoms can exist throughout the cancer trajectory and be associated with the disease itself, cancer treatment, or comorbidities.

Chemotherapy (CTX) is a mainstay of cancer treatment, and most patients will receive chemotherapy at some time during the cancer trajectory. For many, this occurs shortly after diagnosis as part of the initial cancer treatment (Oncology Nursing Society, 2009). A wide range of side effects occurs in conjunction with chemotherapy including pain, depression, fatigue, sleep disturbance, and distress (Honea et al., 2006). Unfortunately, little is known about the symptom experience over time during chemotherapy. Rather, most symptom research uses cross-sectional designs and measures symptom prevalence at a single point in time. The limited studies that examine changes in symptom severity over time are discussed below.

Symptom trajectories during CTX administration have received some attention, but the majority of these studies focused on changes in fatigue and/or sleep disturbance (Berger and Higginbotham, 2000, Braud et al., 2003, Molassiotis and Chan, 2001, Richardson et al., 1998 and Schwartz et al., 2000). Peaks in fatigue were noted immediately after CTX administration (Berger and Higginbotham, 2000 and Schwartz, 2000), two to three days following CTX (Berger

and Higginbotham, 2000, Molassiotis and Chan, 2001 and Schwartz et al., 2000), at neutrophil nadir (Richardson et al., 1998), and with bolus CTX regimens (Richardson et al., 1998). While some studies suggest that fatigue and sleep disturbances may increase over the course of CTX (Berger and Higginbotham, 2000, Danaher et al., 2006, Reyes-Gibby et al., 2007 and Schwartz et al., 2000), inter-individual differences may occur (Berger and Higginbotham, 2000). No studies were found that examined trajectories of pain, depression, and distress during chemotherapy, even though these symptoms often co-occur with fatigue and sleep disturbance.

In addition, no studies have examined the predictors of symptom trajectories during CTX which would reveal inter-individual differences in symptoms over time. Only one study was found that identified the predictors of depression one year after cancer diagnosis in patients with breast, colon, lung, and prostate cancer. Predictors of depression were higher stage of disease, being female, greater number of comorbidities, and less education. However, it is unknown whether these patients underwent CTX (Stommel et al., 2004).

Effective approaches to symptom management are dependent on an understanding of inter-individual differences in the trajectories of patients' symptoms. A National Institutes of Health (NIH) State-of-the-Science Conference convened to discuss the importance of fatigue, pain, and depression related to cancer and its treatment. The panel went on to say that repeated assessments of these symptoms should occur across the cancer and treatment trajectories, as it is not known if symptoms resolve, persist, or exacerbate over time. Without this knowledge, high risk groups cannot be identified and individualized treatments cannot be explored. The panel recommended additional research that examines the occurrence and treatment of these symptoms; specifically, longitudinal studies are needed that examine the severity and duration of these symptoms over time (Patrick et al., 2003).

A modified version of the Symptoms Experience Model (Armstrong, 2003 and Brant et al., 2010) served as the theoretical framework for this study. The model takes into account the global experience of cancer-related symptoms. Antecedents including individual characteristics (age, gender, education, race, religion, marital status) and disease characteristics (type of cancer, stage of disease, type of treatment, comorbidities) provide input into the symptom experience, that are individually defined by the patient. The modified model accounts for the dynamic nature of symptoms that evolve over time, due to symptom interaction of antecedent factors that contribute to the dynamic (changing) nature of the symptom experience. Finally, the modified model can be used to answer questions about the onset and rate of change in symptoms over time or how symptom trajectories change over the course of an illness or in this case, the chemotherapy

treatment trajectory (Brant et al., 2010). These types of questions require longitudinal research designs (Barsevick et al., 2006).

Overall, little is known about inter-individual differences in the trajectories of the majority of symptoms associated with cancer and cancer treatment. In addition, studies of predictors of symptom trajectories that could identify high risk patients are virtually nonexistent. Understanding more about the symptom experience during CTX could lead to the development of risk assessment tools and tailored interventions for patients whose physical and/or psychological symptoms persist.

Therefore, in this study, latent growth curve analyses (LGCA) were used to examine trajectories in the severity of pain, fatigue, depression, distress, and sleep disturbance during the first six cycles of CTX in a sample of outpatients with lymphoma, colorectal, or lung cancer. The specific purposes of this study were: 1) to examine the trajectories of pain, fatigue, depression, distress, and sleep disturbance during the first six cycles of CTX and 2) determine whether individual characteristics (e.g. age, gender, co-morbidities, race/ethnicity type of cancer) predicted each of the symptom trajectories.

Methods

Patients

The sample consisted of 118 patients with lung cancer (n = 55), colorectal cancer (n = 31), or lymphoma (n = 32) who had received CTX at the Hematology-Oncology Centers of the Northern Rockies (HOCNR) outpatient clinic in south central Montana from June 2004 to April 2007. These particular diagnoses were chosen as: 1) the malignancies represent both genders (an antecedent variable in this study) 2) the malignancies are some of the most common cancers treated at oncology clinics, and 3) so little is known about changes in the symptom experiences of these patients. In addition, these three diagnoses were selected to obtain an adequate sample size. Patients were included if they had a new cancer diagnosis; were to undergo an initial course of CTX; and had at least three symptom measures recorded in an electronic database over their first six cycles of CTX, each recorded on day one of the cycle. Patients who underwent CTX for recurrence were excluded. The study was approved by the Inter-institutional review board of Billings, Montana.

Power analysis

Analysis of variance (ANOVA) and repeated measures analysis of variance (RM-ANOVA) are traditional analytical strategies for measuring change over time. These two methods evaluate group change, but they lack the ability to study individual change over time according to group. Latent growth curve analyses have the ability to address these individual changes over time and identify predictor variables that indicate which individuals are most likely to respond in a particular manner over time. In this study, it can identify which individuals are most likely to develop specific symptom patterns over time (Muthen, 2003). The chi-square test for model fit is the most direct measure of power for LGCA, however estimation theory for SEM-type models is asymptotic (based on large samples). While small samples can be used, parameter estimates may be biased, and caution should be used in interpretation of results (Bollen and Curran, 2006).

Data collection tool

Symptoms were assessed using the Patient Care Monitor (PCM), a handheld, electronic tool that recorded information on patients' symptoms in the waiting room prior to each outpatient visit. The PCM is a part of Supportive Oncology Services (SOS), an initiative to improve assessment, documentation, and management of cancer symptoms in adult outpatients (Maxon, 2005). HOCNR was an alpha site for the initiative and began using the PCM in June 2004. Nine self-reported, demographic variables were entered into the PCM during the first outpatient visit: age, gender, type of cancer, stage of disease, number of comorbidities, marital status, education level, race, and religion.

Patients entered symptom data into the PCM at each outpatient visit but not more frequently than once every two weeks. The PCM (1.0) contained a list of 38 symptoms. Only 5 of these symptoms were evaluated in this study. Only data entered on day one of each cycle was used in the analysis.

Each symptom was rated on a 0–10 scale (0 = not a problem, 1 to 3 = mild problem, 4 to 6 = moderate problem, 7 to 9 = severe problem, 10 = as bad as possible). Patients were asked to rate each symptom on a separate screen of an electronic tablet using the time frame of the past week, including today. Pain, fatigue, and sleep disturbance were measured using a single item for each. Depression and distress were measured using 7 and 4 item scales respectively. Normalized T scores (mean 50, SD 10) were automatically calculated from the depression and distress items to create a composite score for each symptom that ranged from 42.92 to 79.89 and 37.93 to 74.56, respectively. Original developers of the PCM computed the normalized T scores using data from a reference sample of a heterogeneous group of oncology patients in Memphis, Tennessee. The T

scores were created so that any given patient could be compared to other patients being treated in an outpatient oncology clinic.

The PCM has undergone extensive psychometric testing and evidence exists to support its validity and reliability (Fortner et al., 2003). Cronbach's alpha for this sample for all five symptoms was 0.86.

Data download and cleaning

PCM records from 530 patients (4287 time points) with a diagnosis of lymphoma, colorectal cancer, or lung cancer were downloaded from the SOS main database to a SPSS file. The dates of data input spanned from June 2004 when the PCM was initiated at the clinic through April 2007. The 530 patients were matched with paper and electronic records at HOCNR and reviewed by hand for eligibility. CTX cycle dates, not included in the PCM data, were inserted at each point of symptom measurement for the 118 eligible patients. Patients were excluded for the following reasons: did not meet inclusion criteria for diagnosis (n = 27), fewer than three data points during CTX (n = 73), treated for relapsed disease (n = 53), no CTX (n = 222), and unavailable CTX cycle data (n = 37).

Data were cleaned and analyzed in SPSS to: 1) delete duplicate cases, 2) assess for missing data, 3) reduce the data set to the eligible sample, 4) reduce the data set to reflect only the variables needed for this study, and 5) flip the data set from a person-period data set (vertical format where each patient visit was entered on a new row) to a person level data set (a standard horizontal format where each patient had multiple and time tagged visits listed on one row). Nomenclature was developed to distinguish each of the visits according to the course number, CTX cycle number, day number of each CTX cycle, and visits not associated with CTX administration. This approach was essential so that day one of each CTX cycle for each patient could be evaluated in the analysis.

Descriptive analyses were completed in SPSS (version 12.0) for Windows for each symptom at each of the six time points to produce means and standard deviations (SD). Data were then exported in a piecemeal process (each individual symptom with predictors) to MPlus 5.0 to conduct LGCA. Because LGCA is an emerging analytic technique in nursing science, some details are provided below.

Statistical analysis

LGCA, implemented in MPlus (Muthen and Muthen, 1998–2007) was used to estimate and evaluate trajectories of symptom change over time and to identify predictor variables associated with the individual growth curve parameters. MPlus uses a structural equation model (SEM) framework for modeling symptom change over time. Symptom change over time is conceptualized as a latent trajectories or growth curves defined by coefficients of linear (intercept, slope) and quadratic polynomial functions and time for each patient (Fig. 1). These individual curve parameters are then used as outcomes in a conditional analysis used to assess the impact of covariates on the individual patient trajectories for each symptom (i.e. depression, distress, pain, fatigue, sleep disturbance) over six CTX cycles. Data were centered on day one of cycle one (i.e. day one cycle one) and set to zero in the analysis, representing the intercept of the growth curve for each patient. The linear rate of constant change (acceleration or deceleration) for each symptom over time is reflected in the slope, and the nonlinear rate of change is reflected in the quadratic parameter. A positive slope indicates an increase in symptom severity over time whereas a negative slope constitutes a decrease. For the quadratic growth trajectory, a positive term represents increasingly faster changes as time goes by and a concave trajectory, whereas a negative coefficient represents a rate of change that decreases faster as time goes by and produces a convex trajectory.

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Initially, unconditional models were estimated to select a functional form (linear or quadratic) for each symptom trajectory. Standard approaches to model evaluation were used (Bentler, 1990, Bentler and Bonett, 1980, Bentler and Yuan, 1999, Browne and Cudeck, 1993 and Hu and Bentler, 1999). Better model fit and power were indicated by a nonsignificant X2 value, a comparative fit index (CFI) > 0.90, a Tucker Lexis Index (TLI) > 0.95, and a root mean square error of approximation (RMSEA) of < 0.06 for a good fit and 0.60 to 0.80 for a fair fit. The standard root mean squared residual (SRMR) < 0.08 was also noted.

Selection of a functional form for each symptom trajectory was evaluated to study the impact of covariates. Each of the ten demographic and clinical characteristics (i.e. age, gender, comorbidities, type of cancer, stage of disease, marital status, education, race, religion, concurrent CTX) was entered one by one into each of the five symptom models (for a total of 50 conditional models) to test whether each of the characteristics could predict the growth parameters. Some characteristics were recoded as dichotomous variables: type of cancer coded as lung (coded as 2) or not (coded as 1), married/partnered or not, Caucasian or other, Christian religion or other, high school diploma or less versus more than high school, and concurrent radiation therapy or not. A nominal significance level of $p < 0.05$ was used to test parameter estimates in all models.

Results

Demographic and clinical characteristics

Table 1 provides a summary of the demographic and clinical characteristics of the sample. The majority of patients were male (55.9%), married/partnered (64%), and white (91.5%) with a mean age of 63.27 (SD 12.45) years. Almost half of the sample had a diagnosis of lung cancer and 44.9% had Stage IV disease. The mean number of comorbidities was 2.5 (range 0–8). The most common comorbidities were hypertension (35.6%), cardiac problems (20.3%), gastric problems (18.6%), and chronic obstructive pulmonary disease (COPD) (13.6%). While most of the patients received CTX alone (72.9%), approximately 15% received concurrent radiation therapy.

Table 1. Demographic and Clinical Characteristics of the Sample (n = 118).

	No	(%)
Demographic characteristics		
Gender		
Male	66	55.9
Female	52	44.1
Age		
24–40	6	5.1
41–55	22	18.6
56–65	29	24.6
65–74	43	36.4
75–84	18	15.3
Marital Status		
Single	9	7.6
Separated	2	1.7

	No	(%)
Divorced	14	11.9
Widowed	17	14.4
Partnered	76	64.4
Race		
Caucasian	108	91.5
Native American	5	4.2
Hispanic	3	2.5
Other	2	1.8
Religion		
Protestant	61	51.7
Catholic	29	24.6
Other	19	16.0
None	9	7.6
Clinical Characteristics		
Type of Cancer		
Lung	55	46.6
Colorectal	31	26.3
Lymphoma	32	27.1
Stage of Disease		
I	6	5.1
II	25	21.2

	No	(%)
III	34	28.8
IV	53	44.9
Comorbidities		
0	4	3.4
1	31	26.3
2	37	31.3
3	25	21.2
4	10	8.5
>4	11	9.3
Treatment		
CTX Alone	86	72.9
Concurrent CTX and XRT	18	15.2
XRT following CTX	14	11.9

CTX = Chemotherapy, XRT = Radiation Therapy.

Symptom severity over six cycles of CTX

The mean symptom severity scores, SDs, and number of patients for each of six time points are provided in Table 2. Distress scores were more intense than depression at time 1 (53.98 versus 51.80) but both remained near the normalized mean of 50 at all time points. Fatigue had a higher mean severity score of 3.90 at time compared to pain (3.00) and sleep disturbance (2.63).

Table 2. Symptom Severity Scores for Each Symptom Over Time.

	Time 1	Time 2	Time 3	Time 4	Time 5	Time 6

	n = 107		*n* = 95		*n* = 94		*n* = 82		*n* = 63		*n* = 54	
Symptom	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Depression	51.80	9.78	51.36	9.49	51.39	8.83	49.25	9.28	49.37	9.15	51.05	9.72
Distress	53.98	11.15	51.71	9.59	49.35	9.68	47.95	9.94	46.91	10.10	48.43	11.10
Pain	3.00	3.05	2.14	2.64	2.16	2.58	1.41	2.13	1.41	2.12	1.91	2.50
Fatigue	3.90	2.62	3.49	2.57	3.81	2.50	3.43	2.52	3.22	2.69	3.44	2.51
Sleep Disturbance	2.63	2.77	2.34	2.66	2.19	2.45	2.09	2.47	1.90	2.33	1.58	2.21

Note: Each time associated with Day 1 of the first 6 cycles of chemotherapy. Depression and Distress based on Normalized T-scores (Mean 50, *SD* 10); Pain, Fatigue, Sleep Disturbance scores range from 0 (not problem) to 10 (as bad as possible).

Unconditional and conditional model fit

Growth curve modeling was conducted for each symptom in MPlus (Muthen and Muthen, 1998–2007), and unconditional models were estimated so that a functional form of change could be selected (linear or quadratic). Table 3 lists the fit statistics for each symptom. Linear models were justified for depression, distress, fatigue, and pain trajectories. For distress and pain, both linear and quadratic models showed a fair fit, but the TLI greater than one indicated a slight over fit for the quadratic model, thus the linear model was chosen. Quadratic change was a better characterization of the sleep disturbance trajectories.

Table 3. Unconditional Model Fit Statistics for Each Symptom.

Symptom	*n*	*df*	X^2	*p*	CFI	TLI	RMSEA	SRMR
Depression								
Linear	113	16	19.030	0.2671	0.989	0.989	0.041	0.092
Quadratic	113	12	17.209	0.1419	0.981	0.976	0.062	0.070
Distress								
Linear	113	16	18.154	0.3150	0.992	0.992	0.035	0.117
Quadratic	113	12	10.228	0.5960	1.000	1.008	0	0.074

Symptom	*n*	*df*	X^2	*p*	CFI	TLI	RMSEA	SRMR
Pain								
Linear	118	16	27.617	0.0350	0.941	0.945	0.078	0.110
Quadratic	118	12	8.568	0.7393	1.000	1.022	0	0.055
Fatigue								
Linear	118	16	26.062	0.3150	0.930	0.935	0.073	0.091
Quadratic	118	12	18.847	0.5960	0.953	0.941	0.070	0.063
Sleep Disturbance								
Linear	118	16	28.363	0.0286	0.879	0.886	0.081	0.141
Quadratic	118	12	11.760	0.4652	1.000	1.003	0	0.064

Note. CFI = comparative fit index, TLI = Tucker-Lewis index, RMSEA = root mean square error of approximation, SRMR = standardized root mean square residual. Model Fit based on desired fit statistics of X^2 test, $p > 0.05$, CFI > 0.95, TLI > 0.95 (over fit > 1) , RMSEA < 0.06 (fair 0.06–0.08); SRMR < 0.08.

Unconditional models of symptom trajectories over time

Fig. 2 shows “spaghetti plots” of observed trajectories for individuals using fatigue as an example. Fig. 2A is a plot of 20 patient trajectories used to demonstrate the high degree of variability in trajectories over time that is often seen in clinical settings. Fig. 2B represents a subset of 5 patient trajectories in which variable patterns can be more easily observed. Patterns are not completely discerned until data are modeled via LGCA. Growth curve estimates for the selected functional forms in the unconditional models are listed in Table 4. For all five symptoms, the mean for intercepts of the unconditional models were all significant ($p < 0.0001$) which indicates a significant difference from zero and the presence of all five symptoms at the initiation of CTX. A significant variance was found for each symptom’s intercept except for sleep disturbance ($p = 0.64$). This finding indicates a high degree of inter-individual variability in the severity of depression, distress, fatigue, and pain existed at the initiation of CTX and that potential predictors for these differences could be evaluated.

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Table 4. Estimates, Z-Scores, and p values for Each Symptom’ s Unconditional Model.

Symptom	Estimate	Z-score	*p*	Variance	Z-score	*p*
Depression						
Intercept	51.197	56.142	$p < 0.0001*$	49.516	4.138	$p < 0.0001*$
Slope	−0.127	−0.693	$p = 0.488$	0.381	0.847	$p = 0.0397$
Distress						
Intercept	51.557	48.292	$p < 0.0001$	84.682	4.724	$p < 0.0001$
Slope	−0.884	−3.869	$p < 0.0001$	1.530	2.174	$p = 0.030$
Pain						
Intercept	2.510	8.657	$p < 0.0001$	6.755	4.454	$p < 0.0001$
Slope	−0.215	−3.039	$p = 0.002$	0.161	2.288	$p = 0.022$
Fatigue						
Intercept	3.805	14.302	$p < 0.0001$	3.592	2.906	$p = 0.004$
Slope	−0.058	−0.783	$p = 0.434$	0.237	2.648	$p = 0.008$
Sleep						
Intercept	2.506	9.953	$p < 0.0001$	2.388	1.853	$p = 0.064$
Slope	−0.122	−0.582	$p = 0.560$	1.033	1.231	$p = 0.218$
Quadratic	−0.007	−0.174	$p = 0.862$	0.029	1.061	$p = 0.289$

Note: Intercept is set to zero.*$p < 0.05$, **$p < 0.0$.

The negative linear slopes for each of the symptoms indicated that on average, symptom severity scores decreased over time. However, the rate of change was significant only for distress (p = 0.03) and pain (p = 0.002). Sleep disturbance had both a negative slope and a quadratic term, indicating a convex trajectory. However, neither the slope nor quadratic term was significant. The slope variances (random effects) were significant ($p < 0.05$) for distress, fatigue, and pain. This finding suggested that potential predictors could be evaluated to identify factors associated with individual differences in rates of change for each of these symptoms.

Conditional models of symptom trajectories over time

Conditional models demonstrated that some demographic and clinical characteristics were significant predictors of inter-individual differences in the intercept as well as the rate of change in symptom trajectories over six chemotherapy cycles. Table 5 includes a summary of the conditional model estimates. No predictors of initial levels of distress were found in the conditional models. The fatigue slope was predicted by a diagnosis of lung cancer; patients with lung cancer experienced an increase in fatigue during CTX. An expression of growth curve parameters with the unconditional curve and conditional curve for lung cancer and fatigue are modeled in Fig. 3. As shown, fatigue severity increased in patients with lung cancer while fatigue severity decreased over time in those diagnosed with colorectal cancer and lymphoma. In addition, patients with more advanced cancer ($p < 0.05$) and a higher number of comorbidities ($p < 0.01$) had higher fatigue severity scores at the initiation of CTX (intercept). An increase in pain severity over time (opposite of the unconditional model that showed a decrease over time) was predicted by concurrent radiation therapy ($p < 0.05$).

Table 5. Significant Estimates, Standard Errors and p Values for Conditional Models.

Condition	Depression		Distress		Pain		Fatigue		Sleep Disturbance	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Cancer Type (Lung or not)										
Intercept	−3.16	1.62	−2.54	1.90	−0.37	0.52	−0.45	0.44	−0.56	0.51
Slope	−0.48	0.36	−0.29	0.45	−0.11	0.14	−0.29∗	0.14	0.21	0.44
Quadratic									−0.02	0.08
Stage										
Intercept	0.22	0.91	0.33	1.05	0.44	0.28	0.54∗	0.24	0.39	0.27
Slope	−0.17	0.21	−0.03	0.26	−0.12	0.08	−0.15	0.08	−0.32	0.23
Quadratic									0.05	0.04
Co-morbidities										
Intercept	0.03	0.55	−0.05	0.64	0.11	0.17	0.36∗∗	0.14	−0.11	0.16
Slope	0.14	0.14	0.12	0.17	−0.06	0.05	−0.07	0.05	0.34∗	0.14

Condition	Depression		Distress		Pain		Fatigue		Sleep Disturbance	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Quadratic									−0.07∗∗	0.03
Race										
Intercept	2.62	2.83	0.16	3.32	0.73	0.94	0.04	0.81	1.14	0.91
Slope	−0.11	0.578	0.03	0.72	−0.20	0.23	−0.02	0.26	−1.66∗	0.75
Quadratic									0.31∗	0.14
Concurrent XRT										
Intercept	−1.24	2.34	0.17	0.11	0.17	0.11	0.20	0.11	0.17	0.11
Slope	0.69	0.56	0.03	0.98	−0.43∗	0.20	0.10	0.23	−0.59	0.63
Quadratic									0.15	0.13

$*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

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The quadratic conditional models for sleep disturbance revealed that comorbidities were a significant predictor of the linear and quadratic curvilinear trajectories. For each increase in the number of comorbidities (e.g., from 2 to 3), there was an increase in the linear slope of 0.34 ($p < 0.05$) and a decrease in the quadratic term of −0.07 ($p < 0.01$). Therefore, patients with an increased number of comorbidities reported more difficulty sleeping over the six cycles of CTX but that this increase leveled off over time, indicated by the small negative quadratic term. Finally, race contributed to linear and quadratic terms for sleep disturbance; Non Caucasian patients reported higher levels of sleep disturbance over time than Caucasian patients ($p < 0.05$).

Discussion

This novel, clinical database study is the first to our knowledge to model trajectories of change over time in some of the most common symptoms (depression, distress, fatigue, pain, and sleep disturbance) reported by oncology patients during the first six cycles of CTX. In addition, findings from this study suggest that some patients may experience more intense and unrelieved symptoms over the CTX trajectory.

Notably, a significant amount of depression, distress, fatigue, pain, and sleep disturbance were present at the initiation of CTX ($p < 0.0001$). This finding suggests that some patients begin CTX with physical and psychological morbidity and may require supportive care early in the disease/treatment trajectory. For all five symptoms, average severity scores decreased over the six cycles of CTX. This finding is consistent with a limited number of studies on distress (anxiety) (Braud et al., 2003), fatigue and sleep disturbance (Gift et al., 2003 and Reyes-Gibby et al., 2007), and depression (Stommel et al., 2004). Furthermore, all symptoms except sleep disturbance had significant variability (random effects) at the initiation of CTX ($p < 0.0001$) and throughout the CTX trajectory ($p < 0.05$), which adds to the existing evidence of significant inter-individual variability in the symptom experience during CTX (Berger, 1998, Berger and Higginbotham, 2000, Braud et al., 2003, Molassiotis and Chan, 2001, Schwartz, 1998 and Schwartz, 2000). However, this study was the first to demonstrate the variability in symptom trajectories across six cycles of CTX.

Distress decreased significantly over time ($p < 0.0001$) which suggests that patients may experience some level of psychological adjustment over the course of CTX. While depression scores showed a negative slope over time, the rate was not significantly different from zero ($p = 0.49$), unlike another study that reported a decrease in depression over time (Stommel et al., 2004). It is important to note that not all of the patients had improvements in their psychological symptoms. The significant variability in both depression and distress suggest that inter-individual differences in patients' experiences exist, as well as in their adjustments to these symptoms. For example, patients with lung cancer compared to those with colorectal cancer and lymphoma reported higher depression scores at the initiation of CTX which approached significance ($p = 0.051$). Unlike other studies (Kurtz et al., 2002 and Miaskowski, 2004), no gender differences in depression were found. A systematic review by Miaskowski (2004) revealed that some studies found a higher incidence of depression in older women and younger men. However, study findings were inconsistent and none were longitudinal (Miaskowski, 2004).

Fatigue had the highest mean intensity of any symptom at the first cycle of CTX (3.9), and was consistent with previous reports (2.36–4.82) (Berger, 1998, Braud et al., 2003, Molassiotis and Chan, 2001 and Schwartz, 2000). However, in contrast to previous reports that suggested that the cumulative effects of CTX (Schwartz, 2000), high doses of CTX (Danaher et al., 2006) and chemoradiation (Reyes-Gibby et al., 2007 and Wang et al., 2006) resulted in cumulative increases in fatigue, fatigue severity in this study decreased over time. These differences may be attributed to the fact that other studies measured fatigue trajectories within CTX cycles for a maximum of three cycles while in this study, symptoms were measured at the beginning of each cycle and for a longer follow-up (i.e. six cycles of CTX). In this study, patients with more comorbidities experienced significantly more severe fatigue at baseline ($p = 0.01$). However, the

linear slope was not significantly different from zero (flat line), which suggests that fatigue levels in patients with a higher number of comorbidities persisted throughout the CTX trajectory compared to other patients. A diagnosis of lung cancer predicted a significant increase in fatigue severity over time ($p = 0.04$) and is inconsistent with previous reports (Gift et al., 2004).

Pain intensity decreased significantly over the six cycles of CTX ($p < 0.01$). However, heterogeneity in trajectories existed, as those who received concurrent radiation therapy reported significant increases in pain over the six cycles of CTX. This finding is consistent with a previous report (Wang et al., 2006) that found that the trajectory of pain increased over time in patients with nonsmall cell lung cancer undergoing chemoradiation. In addition, combined chemoradiation was shown to contribute to increased symptom burden (Cooley et al., 2002 and Sarna et al., 2004), underscoring the importance of tailored symptom management.

Comorbidities in this study were a significant predictor of fatigue at baseline and sleep disturbance over the six CTX cycles. While two cross-sectional studies reported a relationship between comorbidities and the number of overall symptoms (Gift et al., 2004) or the level of symptom distress (Sarna, 1993), no studies were found that reported on the influence that comorbidities can have on sleep disturbance or other symptom trajectories in patients undergoing CTX. In addition, the population is aging in many countries around the world, thereby reflecting an increase in cancer incidence. In relation to this change, older patients with increased numbers of comorbidities are receiving CTX (Balducci, 2003). A population-based study of 15,626 patients with cancer, conducted between 1984 and 1992, revealed that 68.7% of cancer patients had comorbidities and that 32.6% had two or more comorbid conditions (Ogle et al., 2000). While age did not predict symptom severity in this study, the number of comorbidities did. The average number of comorbidities in this study was 2.5 with a range from zero to eight, consistent with previous findings [Ogle et al., 2000]. The influence that these comorbidities will have on CTX-related symptoms over time warrants further investigation.

Because of several limitations, the findings from this study need to be interpreted with caution. First, the sample size was relatively small, and a large percentage of patients had advanced disease, likely due to the inclusion of lung cancer with only 16% of cancers diagnosed at early stage (American Cancer Society, 2008). Second, patients entered data into the PCM at each visit but not more than every two weeks, which resulted in a lack of consistent data on day one of each cycle. For example, some patients had week one and week three data of a four week cycle, but they did not have day one data of each cycle recorded. These omissions resulted in missing data along each of the time points. Also, because this study examined symptoms on day one of each cycle, the symptom experience between cycles (e.g. nadir) was not captured but rather, the

data captured patients in recovery after each cycle. This potentially represents the least intensive symptoms experienced across the chemotherapy treatment trajectory. The growth curves may have been different if data were available at different times during the CTX cycle.

Future opportunities for research are abundant. Studies that capture symptoms within each cycle of CTX and over an entire course of CTX are needed. Understanding finite details within and between cycles can provide a clearer picture of symptom trajectories during CTX. In addition, these findings present more questions about the management of symptoms in patients with multiple comorbidities which are critical in light of an aging population. For example, which comorbidities are most likely to contribute to more severe symptoms during CTX and throughout the cancer experience? Other essential studies will include the impact that symptom trajectories have on distal outcomes such as function. Furthermore, a need exists to conduct studies with more homogenous diagnoses and CTX regimens so that differences in functional forms for symptom trajectories can be identified.

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Conflict of interest

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