Title
Multiple symptoms and symptom clusters in patients with cancer

Author
Kim, Jung Eun Esther

Publication Date
2008-09-19

Peer reviewed|Thesis/dissertation

Multiple Symptoms and Symptom Clusters in Patients with Cancer

by

Jung-Eun Esther Kim

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Program Name

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Abstract

Symptom clusters are stable groups of interrelated symptoms that occur simultaneously. Research on symptom clusters may yield findings that can be used to improve symptom assessment and management. The purposes of this dissertation research were: to evaluate for differences in symptom clusters in a homogeneous sample of oncology patients who underwent radiation therapy (RT) using both the occurrence rates and severity ratings from the Memorial Symptom Assessment Scale (MSAS), as well as to evaluate for differences in symptom factor severity scores between patients with breast and prostate cancer at the end of RT, and to determine the number and types of symptom clusters at three time points (i.e., at the middle of, at the end of, and 1 month after the completion of RT).

A sample of 160 patients who underwent RT was evaluated in this study. Patients completed a clinical questionnaire that obtained information on demographic and clinical characteristics, as well as the MSAS that measured the multidimensional experience of symptoms. Exploratory factor analyses of symptoms were done for selected time points. While the specific symptoms within each symptom cluster were not identical, three very similar symptom factors (i.e., "mood-cognitive" symptom cluster, "sickness-behavior" symptom cluster, "treatment-related" symptom cluster) were identified regardless of whether occurrence rates or severity ratings were used to create the symptom clusters at the end of RT. However, the factor solution derived using the severity ratings fit the data better. Significant differences in all three symptom severity scores were found between patients with breast and prostate cancer. For all three symptom factors, the patients with

breast cancer had higher symptom severity factor scores than the patients with prostate cancer.

Although the number and specific symptoms within each cluster were not identical, three distinct symptom clusters were found across the three time points: “mood-cognitive” symptom cluster, “sickness-behavior” symptom cluster, and “treatment-related” or “pain” symptom cluster. However, differences over time were noted in the “treatment-related” or “pain” symptom clusters. Specifically, at the middle of RT, problem with urination and diarrhea clustered together, while problem with urination and skin problems associated with treatment clustered together at the end of RT. Furthermore, a new symptom cluster (i.e., pain) emerged at 1 month after completion of RT. Future research needs to confirm these findings as well as consider an evaluation of homogeneous samples of patients in terms of both cancer diagnoses and treatments.

TABLE OF CONTENTS

Page

Abstract…….....iii

Tables of Contents……..v

Introduction……1

A REVIEW OF THE PREVALENCE AND IMPACT OF MULTIPLE SYMPTOMS IN ONCOLOGY PATIENTS …….3

Abstract……...4

Introduction…… 5

Methods…… 6

Compare and contrast the characteristics of three instruments used to measure multiple symptoms……7

Rationale for the choice of the three instruments included in this review……..7

M.D. Anderson Symptom Inventory……...8

Memorial Symptom Assessment Scale……....9

Symptom Distress Scale……10

Comparisons among the three symptom assessment instruments…….11

Summary of the prevalence of multiple symptoms……...12

Characteristics of these studies……..12

Characteristics of the study samples……..12

Symptom prevalence in oncology patients receiving active treatment……14

Relationships among select characteristics and multiple symptoms…….14

Relationships among demographic characteristics and symptom severity/distress…….14

Relationships among disease characteristics and treatments and symptom severity/distress…….15

Relationships between multiple symptoms and patient outcomes (Functional Status and/or QOL)……16

Summary and Conclusions……17

References…….20
Table 1……...25
Table 2……...34
Table 3……...……35
Table 4……...……...……36
DIFFERENCES IN SYMPTOM CLUSTERS INDENTIFIED USING OCCURRENCE RATES VERSUS SYMPTOM SEVERITY RATINS IN PATIENTS AT THE END OF RADIATION
THERAPY……40
Abstract……41
Introduction……..42
Methods……45
Participants and Settings……...45
Study Procedures……..46
Instruments……46
Data Analysis……47
Results……48
Demographic and Clinical Characteristics…….48
Symptom Occurrence and Severity……...48
Symptom Clusters Based on Symptom Occurrence……..49
Symptom Clusters Based on Symptom Severity Ratings……..50
Comparison of the Factor Structures Derived from Ratings of Symptom Occurrence and Severity……50
Evaluation of Differences in Symptom Factor Severity Scores Between Patients with Breast and Prostate Cancer……..50
Discussion……..51
References…….55
Table 1……...59
Table 2……...60
Table 3……...61
Table 4……...62

Table 5……...63
Table 6……...64
Table 7……...65
CHANGES IN SYMPTOM CLUSTERS IN PATIENTS UNDERGOING RADIATION THERAPY……66
Abstract……..67
Introduction……68
Methods……..71
Participants and settings……71
Study procedures……71
Instruments……72
Data Analysis……72
Results……74
Patient and Treatment Characteristics……...74
Occurrence and Severity of Symptoms at Each Time Point……74
Symptom clusters at the Middle of RT (Time 1; n=152)……..75
Symptom clusters at End of RT (Time 2; n=160)……76
Symptom clusters at 1 month After Completion of RT (Time 3; n=132)…….77
The similarities and dissimilarities in symptom clusters across time……...78
Discussion……79
References……82
Table 1……...85
Table 2……...86
Table 3……...87
Table 4……...88
Table 5……...89
Table 6……...90
Table 7……...91
Table 8……...92
Conclusion And Recommendation For Future Research……..93
References……95

Introduction

This dissertation contains three papers. The first paper, entitled "A Review of the Prevalence and Impact of Multiple Symptoms in Oncology Patients Undergoing Active Treatment" compares and contrast the characteristics of the three most commonly used instruments to measure multiple symptoms, summarizes the prevalence rates for multiple symptoms in studies of oncology patients receiving active treatment; describes the relationships among selected demographic, disease, and treatment characteristics and multiple symptoms; as well as describes the relationships between the occurrence of multiple symptoms and patients outcomes (i.e., functional status, quality of life) [In press: Journal of Pain and Symptom Management].

The second paper, entitled "Differences in Symptom Clusters Identified Using Occurrence Rates Versus Symptom Severity Ratings in Patients At the End of Radiation Therapy," reports findings that three very similar symptom factors (i.e., "mood-cognitive" symptom cluster, "sickness-behavior" symptom cluster, "treatment-related" symptom cluster) were identified regardless of whether occurrence rates or severity ratings were used in the exploratory factor analyses. However, the factor solution derived using the severity ratings fit the data better. In addition, for all three symptom factors, the patients with breast cancer had higher symptom severity factor scores than the patients with prostate cancer.

The third paper, entitled "Changes in Symptom Clusters in Patients Undergoing Radiation Therapy," reports that while the number and specific symptoms within each cluster are not identical, three distinct symptom clusters were found across the three time points: "mood-cognitive" symptom cluster, "sickness-behavior" symptom cluster, and

"treatment-related" or "pain" symptom cluster. However, differences over time were noted in the "treatment-related" or "pain" symptom clusters.

The dissertation concludes with a section that summarizes the findings across the three papers. In addition, the final chapter summarizes the directions for future research.

A Review of the Prevalence and Impact of Multiple Symptoms in Oncology Patients

Jung-Eun Esther Kim, RN, MS, PhD(c)[1]

Marylin J. Dodd, RN, PhD, FAAN[1]

Bradley E. Aouizerat, PhD[1]

Thierry Jahan, MD[2]

Christine Miaskowski, RN, PhD, FAAN[1]

[1]Schools of Nursing and [2]Medicine

University of California, San Francisco

In press, *Journal of Pain and Symptom Management*

Abstract

Findings from several studies suggest that oncology patients undergoing active treatment experience multiple symptoms and that these symptoms can have a negative effect on patient outcomes. However, no systematic review has summarized the findings from studies that assessed multiple symptoms in these patients. Therefore, the purposes of this review were to: 1) compare and contrast the characteristics of the three most commonly used instruments to measure multiple symptoms; 2) summarize the prevalence rates for multiple symptoms in studies of oncology patients receiving active treatment; 3) describe the relationships among selected demographic, disease, and treatment characteristics and multiple symptoms; and 4) describe the relationships between the occurrence of multiple symptoms and patient outcomes (i.e., functional status, quality of life). Only 18 studies were found that met the inclusion criteria for this review. The majority of the studies were cross-sectional with sample sizes that ranged from 26 to 527. Approximately 40% of patients experienced more than one symptom. However, little is known about the relationships between demographic and clinical characteristics and the occurrence of multiple symptoms. Findings from this review suggest that the occurrence of multiple symptoms is associated with decreased functional status and quality of life. However, given the large number of oncology patients who undergo active treatment each year, additional research is warranted on the prevalence and impact of multiple symptoms. Only when this descriptive research is completed with homogenous samples of patients in terms of cancer diagnoses and treatments can intervention studies for multiple symptoms be developed and tested.

KEY WORDS: multiple symptoms, symptom clusters, patient outcomes, symptom assessment, symptom prevalence

Introduction

Patients with cancer can undergo a variety of treatments (e.g., surgery, radiation (RT), chemotherapy (CTX), hormonal therapy) either singly or in combination. While these treatments improve survival, they can produce a variety of symptoms. In fact, findings from several studies suggest that patients receiving active treatment (1,2) experience multiple symptoms simultaneously. For example, in one of the first studies of multiple symptoms (3), women with ovarian cancer reported an average of 10.2 symptoms (range of 0 to 25 concurrent symptoms). More recently, Donovan and colleagues (4) found that 74% of women who received CTX for ovarian cancer reported 13.4 concurrent symptoms.

When these symptoms are not managed effectively, they can cause interruptions or cessation of cancer treatment (5) or decrease patients' level of adherence with a treatment regimen (6-12). In addition, unrelieved symptoms can have a negative impact on patients' functional status, mood, and quality of life (QOL) (5,13-16).

Given the negative outcomes associated with multiple symptoms, it seems prudent that clinicians and researchers should evaluate the prevalence and impact of multiple symptoms in oncology patients undergoing active treatment. These types of evaluations could be used to guide the development and testing of interventions for multiple symptoms. However, no systematic review has summarized the findings from studies that evaluated multiple symptoms in oncology patients receiving active treatment. Therefore, the purposes of this review were to: 1) compare and contrast the characteristics of the three most commonly used instruments to measure multiple symptoms; 2) summarize the prevalence rates for multiple symptoms in studies of oncology patients receiving active treatment; 3) describe the relationships among selected demographic, disease, and treatment characteristics and multiple symptoms; and 4) describe the

relationships between the occurrence of multiple symptoms and patient outcomes (i.e., functional status, QOL).

Search Methods

For this review, systematic electronic searches of MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and PsycINFO databases were performed. The searches were restricted to adults with cancer and English language articles. The search terms used were symptom, multiple symptoms, cancer, cancer treatment, QOL, and symptom assessment instruments. The searches were limited to the years 1990 through 2007 because no studies of multiple symptoms in oncology patients were published prior to 1990.

Studies were included if they: evaluated the prevalence of multiple (> one) symptoms; used one of three valid and reliable instruments (i.e., the Symptom Distress Scale (SDS; (17)), the M.D. Anderson Symptom Inventory (MDASI; (18)), the Memorial Symptom Assessment Scale (MSAS; (19)) to evaluate multiple symptoms; and included adult oncology patients who were receiving active treatment in inpatient or outpatient settings. Studies were excluded if they: evaluated multiple symptoms in patients who were receiving palliative or hospice care; measured the side effects of treatment; and/or used QOL instruments or symptom specific instruments to measure multiple symptoms.

The retrieved studies were reviewed by the first author (J-EK) initially to determine if they met the inclusion and exclusion criteria. Then the reference lists of selected studies were manually searched to identify any additional studies. Based on the search parameters, 76 abstracts were identified for this review. A total of 69 studies addressed some aspect of multiple symptoms. Fifty-one abstracts were eliminated because they used instruments without established validity and reliability (i.e., Canberra Symptom Score Card, Chemotherapy Symptom

Assessment Scale, a Computerized Symptom Assessment Instrument, Pain and Symptom Assessment Record, Symptom Experience Scale, the Symptom Monitor, the Symptom Reporting Tool, the modified Edmonton Symptom Assessment System (ESAS), the MSAS Modified for family caregivers). Therefore, 18 studies of multiple symptoms met the prespecified inclusion/exclusion criteria (see Table 1).

COMPARE AND CONTRAST THE CHARACTERISTICS OF THREE INSTRUMENTS USED TO MEASURE MULTIPLE SYMPTOMS

Rationale for the choice of the three instruments included in this review - The ideal instrument to measure multiple symptoms should include those symptoms that occur frequently and are most distressing to patients. In addition, it should be relatively short, easy for patients with limited educational backgrounds to understand, and applicable for both clinical practice and research (5,18). Ideally, the instrument should be available in multiple languages.

Several instruments are available to measure multiple symptoms including the ESAS (20,21), the MDASI (18), the MSAS (19), the Oncology Treatment Toxicity Assessment Tool (OTTA) (2), the Rotterdam Symptom Checklist (RSCL) (22), the SDS (17,23), and the Worthing Chemotherapy Questionnaire (24). All of these instruments are comprehensive and have good psychometric properties. For this review, the ESAS, RSCL, OTTA, and the Worthing Chemotherapy Questionnaire were excluded for a number of reasons. The ESAS was designed to assess symptoms in palliative care patients. The RSCL was designed to assess symptoms in cancer patients who participated in a clinical trial. Both the OTTA and the Worthing Chemotherapy Questionnaire assess treatment-related side effects.

It should be noted that several symptom specific instruments and QOL scales can be used to evaluate the presence and severity of a single symptom or pairs of symptoms such as fatigue

(e.g., Piper Fatigue Scale (25)), depression and anxiety (e.g., Hospital Anxiety and Depression Scale (26)), and nausea and vomiting (e.g., Rhodes Index of Nausea and Vomiting, (27)). While symptom specific scales provide valuable information on the multiple dimensions of a single symptom and many QOL instruments contain items that evaluate multiple symptoms often as part of physical and psychological subscales, they capture different aspects of the symptom experience compared to valid and reliable instruments that were designed to capture the occurrence, severity, and/or distress of multiple concurrent symptoms in patients undergoing active cancer treatment. In addition, most of the multidimensional QOL instruments contain only a limited number of common symptoms (19). Therefore, in this review, only those studies that used one of three symptom inventories (i.e., SDS, MDASI, MSAS) were reviewed because they are valid and reliable measures that provide information about a large number of physical and psychological symptoms that are assessed concurrently. The psychometric properties of these three instruments are summarized in Table 2.

M.D. Anderson Symptom Inventory - The MDASI was developed by the Pain Research Group at the University of Texas M. D. Anderson Cancer Center (18). The original tool included 26 symptoms. However, 13 items (i.e., not able to get things done, weak, worrying, nervous, irritable, sick, constipation, attention, bloated, cough, diarrhea, mouth sores, bleeding) were deleted because they were deemed redundant or had low prevalence rates in oncology patients. The MDASI measures the severity of 10 physical symptoms (i.e., pain, fatigue (tiredness), disturbed sleep, dry mouth, lack of appetite, nausea, vomiting, drowsy, shortness of breath, numbness or tingling), 3 psychological symptoms (i.e., problem with remembering things, feeling sad, distress), and 6 interference items (i.e., general activity, mood, work, relations with other people, walking, enjoyment of life).

Each symptom is rated on an 11-point numeric rating scale (NRS) with 0 indicating "not present" and 10 indicating "as bad as you can imagine". Each symptom on the MDASI is rated at its worst in the past 24 hours. Six interference items that describe how much all of the symptoms interfere with common activities are rated using an 11-point NRS (i.e., 0 "does not interfere to 10 "interferes completely"). Of note, the final 13 symptoms explained 64% of the variance in symptom interference. Validity of the MDASI was determined using factor analysis and internal reliabilities ranged from 0.82 to 0.87 for the symptom items and from 0.91 to 0.94 for the interference items (18).

Memorial Symptom Assessment Scale - The MSAS is a self-report instrument that measures, using Likert scales, the severity (1 (mild) to 4 (very severe)), frequency (1 (rarely) to 4 (almost constantly)), and distress (0 (not at all) to 4 (very much)) of 26 physical and 6 psychological symptoms (i.e., difficulty concentrating, feeling sad, worrying, feeling nervous, feeling irritable, and "I don't look like myself") in cancer patients during the previous 7 days (19). It provides multidimensional information about a large number of symptoms that are experienced by oncology patients. Twenty-four symptoms are evaluated in terms of all three dimensions (i.e., severity, frequency, distress), and 8 symptoms (i.e., mouth sores, change in the way food tastes, weight loss, constipation, hair loss, swelling of arms or legs, changes in skin, "I don't look like myself") are evaluated for only severity and distress.

The MSAS is scored into physical and psychological subscales as well as a Global Distress Index (GDI). The GDI is made up of four prevalent psychological symptoms (i.e., feeling sad, worrying, feeling irritable, feeling nervous) and six prevalent physical symptoms (i.e., lack of energy, dry mouth, lack of appetite, pain, constipation, feeling drowsy). The GDI provides a measure of global symptom distress.

The physical symptom subscale score (MSAS-PHYS) is the average of the frequency, severity, and distress of the 12 most prevalent physical symptoms. The psychological symptom subscale score (MSAS-PSYCH) is the average of the frequency, severity, and distress of the six most prevalent psychological symptoms. The total MSAS (TMSAS) score is the average of the three symptom scores for all 32 symptoms. The MSAS has demonstrated validity and reliability in patients with cancer (19,21). Concurrent validity of the MSAS was demonstrated through a strong positive correlation with the Functional Living Index for Cancer (FLIC) QOL measure and with the Karnofsky Performance Status (KPS) Score (19). Construct validity was determined through comparisons of MSAS scores among different cancer diagnoses. Discriminant validity was determined by comparing the MSAS scores of inpatients and outpatients (19).

Symptom Distress Scale - The SDS is a measure of symptom distress defined as "the degree of discomfort from specific symptoms being experienced as reported by the patient" (17). It provides a measure of the severity of symptom distress and was one of the first valid and reliable instruments developed for symptom assessment in oncology patients. This 13-item self-report instrument assesses the level of symptom distress for 13 symptoms (i.e., pain, fatigue, insomnia, lack of appetite, nausea, bowel dysfunction, shortness of breath, coughing, poor activity, difficulty with concentration, mood, altered appearance, poor outlook). In addition, the frequency of occurrence of pain and nausea are reported separately.

Each item is scored on a 5-point Likert scale (i.e., 1= the least amount of distress associated with a symptom to 5 = extreme distress associated with a symptom) that measures the distress associated with each symptom at that moment or for that day. Items rated $\geq$ 3 indicate serious distress. A total score is obtained by summing the scores for the 13 items and can range from 13 (little distress) to 65 (severe symptom distress). A total score of $\geq$ 25 indicates moderate

distress and a score of $\geq$ 33 indicates severe distress that requires immediate intervention (23). The SDS has demonstrated acceptable internal consistency (Cronbach $\alpha > 0.80$) and test-retest reliability in patients with lung cancer (28) as well as content, construct, and criterion validity.

Comparisons Among the Three Symptom Assessment Instruments - The specific symptoms that are measured by each of these instruments were summarized in Table 3. While these three instruments purport to measure "common" symptoms in oncology patients, the number as well as the specific symptoms that are assessed vary across the three instruments. Only eight symptoms (i.e., pain, fatigue, difficulty sleeping, lack of appetite, nausea, shortness of breath, difficulty with concentration, mood/sad) are measured by all three instruments.

Another difference among these three instruments is the aspect of the symptom experience that is assessed. The SDS focuses on the distress associated with each symptom, which is suggested to be a proxy for symptom severity. While the MDASI measures the severity of each symptom individually, interference is assessed for all of the symptoms collectively. In contrast, the MSAS measures frequency, severity, and distress for each symptom. However, the MDASI and the MSAS measure symptom severity using different scales. In addition, the instructions for the MDASI ask patients to rate symptoms at their worst, while the MSAS asks for ratings of average symptom severity.

Although both the SDS and the MSAS measure symptom distress, it is assessed using different scales (i.e., a 1 to 5 scale on the SDS versus a 0 to 4 scale on the MSAS). Another difference is that the timeframe for symptom assessment varies across the three instruments (i.e., SDS and MDASI = "at that moment or on that particular day"; MSAS = "past week").

The SDS and the MDASI take 5 to 10 minutes to complete. No information is available on how long it takes to complete the MSAS. The psychometric properties of these three

instruments are well established. Factor analysis of the MSAS and MDASI confirmed the factor structure of these instruments (18,19). The Cronbach's alphas for the three instruments are comparable (see Table 2).

All three instruments were developed in the United States. The SDS and the MDASI have been translated and validated in several languages. Translations of the SDS are available in Dutch, Italian, Spanish, Swedish, Korean, and Taiwanese. The MDASI has been translated into Chinese, Korean, Japanese, Greek, Russian, and Filipino. No information was found on translations of the MSAS.

SUMMARY OF THE PREVALENCE OF MULTIPLE SYMPTOMS

Table 1 provides a summary of the 18 studies that evaluated multiple symptoms in adult oncology patients receiving active treatment. Of these 18 studies, six (37%) used the SDS (29-34), seven (39%) used the MDASI (4,18,35-39), and five (28%) used the MSAS (3,19,21,40,41).

Characteristics of these studies - Sixteen studies (89%) used a cross-sectional design, while two (11%) were longitudinal. Prospective data were collected in all of the cross-sectional studies. One of the longitudinal studies (33) used a prospective design and assessed multiple symptoms and symptom distress at the initiation of treatment and 1 and 2 months later. The other longitudinal study (34) evaluated multiple symptoms at the start of treatment and again at 3 and 6 months. Both of these longitudinal studies used the SDS to describe the patterns of symptom distress in patients with lung cancer.

Characteristics of the study samples - Sample sizes for the 18 studies varied widely and ranged from 26 (33) to 527 participants (18). Five studies (28%) had sample sizes of less than 100 (29,30,32,33,40). The remaining 13 studies (72%) had sample sizes that ranged from 117 to 527. All of these studies recruited convenience samples from multiple sites.

The mean age of the participants was 59.1 with a range from 47.0 to 66.9 years. About 78% of the studies (n=14) enrolled both genders and overall 52% of the participants were male. Four studies measured symptoms only in women with lung or ovarian cancer (3,4,30,42).

Approximately, 44% of the studies (n=8) were conducted in United States (3,4,18,19,21,29,30,34). Across these 8 studies, the majority (73%) of the participants were Caucasian (range 63% to 94%). Of the remaining 10 studies, three were done in Canada (31,32,40), two in China (36,41), one in Sweden (33), one in Japan (35), one in Russia (37), one in the Philippines (38), and one in Taiwan (39).

Fifty percent of the studies (n=9) collected data from heterogeneous samples of patients with a variety of cancer diagnoses (18,19,21,31,35,37,38-40). Regarding the site of cancer, four studies (22%) assessed symptoms only in patients with lung cancer (30,32-34), two (11%) assessed patients with ovarian cancer (3,4), and one (6%) assessed patients with gastrointestinal cancers (41). One study (6%) failed to provide information on cancer diagnosis (29).

Among the 6 studies that assessed multiple symptoms using the SDS, four studies evaluated patients with lung cancer (30,32-34); one assessed a heterogeneous sample (31); and one failed to describe the patients' cancer diagnoses (29). In the seven studies that used the MDASI, five recruited patients with a variety of cancer diagnoses (18,35,37-39), one recruited only patients with ovarian cancer (4), and one recruited only patients with lung cancer (36). Of the five studies that used the MSAS, one study assessed patients with prostate, colon, breast, and ovarian cancers (19), one assessed patients with ovarian cancer (3), one with gastrointestinal cancers (41), and two evaluated heterogeneous samples (21,40).

The patients' stage of disease varied across these studies. Four studies (29,33,40,41) did not provide any information on stage of disease while three (19,21,35) found that the presence of

metastatic disease was associated with an increased number of symptoms. Across the remaining 11 studies, 52% of the patients (range 12% to 87%) had stage III-IV disease. In sixteen studies, patients were receiving active treatment with CTX, RT, biotherapy, surgery, or a combination of treatments. No information on the specific treatments was provided in two studies (19,33).

Symptom Prevalence in Oncology Patients Receiving Active Treatment - Table 4 provides a summary of the prevalence rates for the various symptoms in each of the studies as well as a mean prevalence rate across these studies. Symptom prevalence rates ranged from 11% for sore mouth to 62% for fatigue. The ten most prevalent symptoms across the 18 studies were fatigue (62%), worrying (54%), feeling nervous (45%), dry mouth (42%), insomnia (41%), feeling sad/mood (39%), feeling irritable (37%), pain (36%), drowsiness (36%), and distress (34%). The prevalence rates for these 10 symptoms ranged from 34% to 62%. Across the 18 studies, 40% to 61% of patients experienced more than one symptom (30,36) and 22% to 30% of patients experienced more than 5 concurrent symptoms (18,36,37).

RELATIONSHIPS AMONG SELECT CHARACTERISTICS AND MULTIPLE SYMPTOMS

Relationships Among Demographic Characteristics and Symptom Severity/Distress - The relationships among a variety of demographic characteristics and the type of symptom experienced were examined in only 4 studies (19,21,31,41). However, the findings from these studies are inconsistent. Only two studies evaluated for age differences in the severity of symptom distress. In one study (31), age was weakly correlated with symptoms distress ($r = -0.11$, $p < 0.02$) and younger patients tended to have higher levels of symptom distress than older patients. In contrast, Yan and Sellick (41) found that patients in their older age group ($\geq$ 70 years) reported higher symptom distress scores than those in their younger age group (< 40 years).

In addition to age, gender differences in symptoms distress (31) and symptom prevalence (19) were evaluated in only two studies. In one study that used the SDS (31), women reported higher symptom distress scores than men ($p < 0.041$). In another study that used the MSAS (19), no gender differences were found in any of the symptom prevalence rates.

Relationships Among Disease Characteristics and Treatments and Symptom Severity/Distress - The relationships between site and stage of cancer and symptom severity and distress were evaluated in 5 studies (21,30,31,36,41). In one study (31), patients with lung cancer had higher symptom distress scores than either women with breast cancer or males with genitourinary cancer. In a study of Chinese patients (36), fatigue and sleep disturbances were the most common symptoms in patients with breast and lung cancer, whereas fatigue and lack of appetite were the most common symptoms in patients with gastrointestinal cancer. In another study of symptoms, psychological distress, and QOL in Chinese patients with newly diagnosed gastrointestinal cancer (41), patients with liver cancer had higher symptom frequency, severity, and distress scores than patients with all other gastrointestinal cancer diagnoses. Findings across these 3 studies suggest that patients with recurrent (30), metastatic (21), or advanced stage of disease (31) reported the most severe and distressing symptoms.

The type of cancer treatment appeared to influence the prevalence and severity of multiple symptoms. However, of the 18 studies, only three evaluated the prevalence of symptoms and symptom severity/distress in relationship to type of cancer treatment (29,30,34). In a study that compared mean SDS scores of patients who received CTX versus RT (29), patients who received CTX reported higher SDS scores especially for tiredness and poor appearance compared to those who received RT. In another study (30), patients who received CTX reported higher symptom distress scores that patients who underwent surgery. More

recently, the prevalence of distressing symptoms was evaluated in patients who received a variety of treatments for lung cancer (34). At entry into the study, the three most distressing symptoms for patients with surgery were pain, fatigue, and insomnia; for patients with RT they were fatigue, lack of appetite, and nausea; for patients with CTX they were fatigue, insomnia, and lack of appetite; and for patients with combined treatments they were fatigue, pain, and insomnia. Patients who received only RT reported a significantly higher number of symptoms across time compared to the other three groups.

Symptom prevalence rates appear to differ based on the settings of care. Findings from two studies (3, 19) found that inpatients reported a higher number of symptoms than outpatients. The mean number of symptoms for inpatients with ovarian cancer was 11.2 (range of 1 to 25) compared to 7.4 for outpatients (range of 0 to 16, (3)). In another study (19), the mean number of symptoms for inpatients with various cancers was 13.5 compared to 9.7 for outpatients.

RELATIONSHIP BETWEEN MULTIPLE SYMPTOMS AND OUTCOMES

Relationships Between Multiple Symptoms and Patient Outcomes (Functional Status and/or QOL) - The relationships between symptoms and functional status and QOL were examined in only five (28%) of the 18 studies (19, 21, 30, 31, 41). Two studies examined the relationships between the number of symptoms, symptom distress, and functional status (19, 30). In a study of symptom distress and functional status in women with lung cancer (30), as symptom distress increased, functional status decreased. The other study (19) reported that the higher the number of symptoms, the poorer the patients' functional status. Patients with KPS scores of $\leq$ 80 reported 14.8 symptoms while patients with KPS scores of > 80 reported only 9.2 symptoms ($p<0.0001$).

Four studies found that patients who reported a larger number of symptoms or symptom distress had poorer QOL scores (19, 21, 30, 41). Sarna (30) reported that higher levels of symptom distress in women with lung cancer were significantly correlated with decreases in both the physical and psychological dimensions of QOL. In another study of patients newly diagnosed with gastrointestinal cancers (41), those who reported lower levels of symptoms distress reported higher QOL scores.

Findings from two studies that used the MSAS (19, 21) suggest that a higher number of symptoms was strongly correlated with poorer QOL. In one study of 243 adults with various types of cancer (19), significant negative correlations were found between the number of symptoms and patients' overall QOL ($r= -0.67$, $p< 0.0001$). In addition, higher symptom distress scores were associated with increased psychological distress. Another study (21) confirmed that a higher number of symptoms was associated with a poorer QOL. Finally, two studies (31, 34) found that symptom distress at diagnosis was a significant predictor of symptom distress over time, as well as decreased functional status, poorer QOL, and decreased survival. Cooley et al. (34) reported that baseline symptom distress predicted nine distressing symptoms at 3 months and seven distressing symptoms at 6 months in 117 patients with newly diagnosed lung cancer.

Summary and Conclusions

This review is the first to evaluate the prevalence of as well as the factors associated with the occurrence of multiple symptoms in adult oncology patients undergoing active treatment. Findings from a limited number of studies suggest that the prevalence rates for multiple symptoms are relatively high. Across 18 studies, more than 50% of oncology patients reported experiencing fatigue and worry. Of note, fatigue was the most prevalent symptom across the 18 studies. In addition, findings from these studies suggest that multiple symptoms are associated

with decreases in functional status and QOL. The occurrence of multiple symptoms may be related the disease itself, active treatment, sequelae of treatment, or comorbid conditions. Finally, the experience of multiple symptoms is associated with higher levels of symptom distress.

Several limitations across these studies must be noted. First, of the 18 studies, 89% were descriptive and cross-sectional. Therefore, little is known about how multiple symptoms change across the course of a patient's treatment trajectory. Longitudinal studies are needed to describe the trajectories of multiple symptoms in oncology patients undergoing active treatment. Without these descriptive, longitudinal studies, it will be difficult to plan intervention studies to manage multiple symptoms.

Second, all of the studies in this review used convenience samples which limit the generalizability of the study findings. In addition, the majority of the patients were Caucasian. Future research should evaluate the prevalence and severity of multiple symptoms in more ethnically diverse samples because some data suggest that differences in symptom severity and distress do occur across ethnic groups (43-45). Third, relationships between various patient and disease characteristics and multiple symptoms warrant additional investigation since only a few studies have examined this aspect.

Perhaps one of the major areas that needs to be addressed in future studies of multiple symptoms is which symptoms should be included on any comprehensive symptom inventory. The number of symptoms in the three instruments included in this review range from 13 to 32 symptoms and only 8 of these symptoms are common across instruments. However, it is not clear if any of these instrument's list of symptoms is comprehensive and appropriate for all cancer diagnoses and treatments. As equally important question that warrants consideration is

what symptom dimensions (i.e., severity, frequency, and/or distress) should be assessed to capture the patient's experience of multiple symptoms.

Clinical experience suggests that cancer and its treatment is marked by the occurrence of multiple symptoms that influence the patient's ability to continue usual activities and enjoy life. However, a very limited number of studies have attempted to measure the prevalence and impact of multiple symptoms in patients with cancer. The gaps in knowledge identified in this review warrant additional research. That said, within the past 5 years, the concept of a symptom cluster has emerged as an important area in symptom management research (46-48). However, this concept is still in its infancy and warrants additional concept clarification and refinements in its methodology and approaches (49). Therefore, at the present time studies of multiple symptoms need to continue particularly in samples of patients with homogeneous cancer diagnoses and cancer treatments. These types of studies will guide the development of intervention studies as well as symptom cluster research.

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Table1. Summary of the Studies of Multiple Symptoms in Adult Oncology Patients

Author Purpose	Sample characteristics	Design Instruments	Major Findings
Chang et al. (2000) To assess symptom prevalence and symptom intensity and their relationship to quality of life	n=240 Age: 65.4 years Female: 4% Ethnicity: 63% white Various cancers Stage: 69% metastasis Treatment: no specific information	Cross-sectional MSAS FACT-G BPI	Median number of symptoms was 8. Most prevalent symptoms were lack of energy (62%), pain (59%), dry mouth (54%), shortness of breath (50%), and difficulty sleeping (45%). Patients with moderate pain had a median of 11 symptoms. Patients with moderate fatigue had a median of 13 symptoms. Patients with metastatic disease experienced more severe and distressing symptoms. Patients with moderate pain and fatigue experienced nausea, shortness of breath, and lack of appetite. Number of symptoms positively correlated with extent of disease. The prevalence of weight loss, shortness of breath, constipation, problem with sexual interest, and difficulty with swallowing was higher for inpatients than outpatients. The higher the number of symptoms the lower the patients' QOL.
Chen & Tseng (2006) To understand which cancer-related symptoms clustered together To test the conceptual meanings of the revealed symptom clusters	n=151 Age: 50 years (range:18-79) Female: 40% Ethnicity: 100% Taiwanese Various cancers Stage: 50% stage lll-lV Treatment: 48.3% CTX	Cross-sectional MDASI HADS-D KPS	Mean number of concurrent symptoms was 8.3. Most prevalent symptoms were dry mouth (84.1%), fatigue (82.1%), lack of appetite (76.2%), pain (72.8%), and disturbed sleep (72.2%). Five most severe symptoms were fatigue, dry mouth, distress, disturbed sleep, lack of appetite, and pain. Symptoms interfered most often with working, enjoyment of life, and general activity.

Author Purpose	Sample Characteristics	Design Instruments	Major Findings
Cleeland et al. (2000) To develop the M.D. Anderson Symptom Inventory	n= 527 inpatients and outpatients Age: 55 years Female: 55% Ethnicity: not reported Various cancers Stage: 29% metastasis Treatment: 56% CTX, 23% biotherapy	Cross-sectional MDASI ECOG-PS	Most prevalent symptoms in the moderate to severe range were fatigue (59%), not able to get things done (51%), weakness (50%), worrying (43%), disturbed sleep (41%), dry mouth (37%), and pain (34%). Over 25% of the patients experienced 18 symptoms at moderate or severe levels. The two symptoms that contributed the most to interference were fatigue and sadness. Patients who received CTX reported a higher level of nausea, lack of appetite, and emesis compared to patients who did not received cancer treatment.
Cooley et al. (2003) To describe the most distressing symptoms in adults newly diagnosed with lung cancer To describe the prevalence of symptoms in adults receiving treatment for lung cancer To examine changes in symptom prevalence in adults receiving treatment for lung cancer over time To identify patient and clinical characteristics related to symptom distress	n=117 Age: 64.7 years (42-84) Female: 46% Ethnicity: 91% white Lung cancer Stage: 86% early and regional, 12% advanced stage Treatment: 7% CTX, 11% RT, 38% surgery, 44% combined therapy	Longitudinal T1 at baseline, T2 at 3 months, and T3 at 6 months SDS	At T1, the five most distressing symptoms were fatigue (64%), frequent pain (56%), insomnia (49%), lack of appetite (43%), and severity of pain (37%). The prevalence of these symptoms decreased over time. Adults with lung cancer experienced an average of 4 highly distressing symptoms at entry into study and this number decreased to 3 at 3 and 6 months. At T1, patients who received RT reported a higher mean number of symptoms than those who received CTX or combined therapy. Mean number of distressing symptoms varied significantly among treatment groups at T1 but not at T2 and T3. The mean number of highly distressing symptoms decreased over time in the combined treatment groups as compared to the other treatment groups. Patient and clinical characteristics did not predict distressing symptoms consistently. Symptom distress at T1 was the best predictor of symptom distress at T2 and T3.

Author Purpose	Sample Characteristics	Design Instruments	Major Findings
Degner & Sloan (1995) To describe levels of symptom distress in a general ambulatory population To describe the factors associated with symptom distress	n=434 outpatients Age: 59.3 years (range: 45-73) Female: 48% Ethnicity: Canadian Various cancers Stage: 29% early, 34% advanced stage Treatment: 34% CTX, 63% RT, 49% surgery	Cross-sectional SDS	Level of symptoms distress in ambulatory patients was low. The mean symptom distress score was 23.0 (range of 13 to 50). Lung cancer patients had the highest levels of symptom distress scores. The most distressing symptoms were fatigue (39%), insomnia (31%), pain frequency (24%), pain intensity (19%), and poor outlook (24%). Women and patients with advanced disease reported higher levels of symptom distress. Older patients had less symptom distress than younger patients. Higher symptom distress at baseline predicted shorter survival.
Donovan et al. (2005) To describe the symptom experiences of women with ovarian cancer To describe the extent to which women and clinicians communicate about symptoms To evaluate whether communication was associated with patients' confidence in managing symptoms	n=279 Age=55.5 years (range: 22-91) Female:100% Ethnicity: 94% white Ovarian cancer Stage: 81% stage lll-lV Treatment: 57% CTX, 10% RT	Cross-sectional MDASI-modified to include symptoms specific to ovarian cancer (22 symptoms) SRQ A single question designed to measure discussion of symptoms and adherence to treatment recommendations Daily Coping Inventory	Mean number of concurrent symptoms was 12. These symptoms were in the moderate to severe range. Five "most noticed" symptoms in the past week were fatigue (59%), bowel disturbances (37%), pain (27%), neuropathy (26%), and abdominal bloating (25%). Five most severe symptoms were fatigue, bowel disturbances, sleep disturbances, memory problems, and peripheral neuropathy. Mean severity of symptoms identified as noticed most was 7. 61% of the patients had discussed their most noticed symptom with a clinician in the past month. 50% of the patients reported receiving symptom management recommendations from clinicians. 76% of the patients identified at least one coping strategy to manage their most noticed symptom.

Author Purpose	Sample Characteristics	Design Instruments	Major Findings
Holmes (1990) To identify any differences in the degree of symptom distress between patients undergoing CTX and RT	n=51 22 (43%) with CTX and 29 (57%) with RT No information provided about demographic and clinical characteristics	Cross-sectional SDS based on a linear analogue self assessment (LASA) (0-100 mm)	The most distressing symptoms were tiredness (59%), appearance (51%), concentration (43%), mood (43%), and pain (37%) in both patients with CTX and RT. The common causes of distress in patients with CTX were tiredness (64%), difficulty with concentration and mood (55%), altered appearance (55%), poor activity (36%), and pain (27.3%). The common causes of distress in patients with RT were tiredness (55%), altered appearance (48%), pain (45%), constipation (41%), and poor appetite (38%). The mean SDS score for patients on CTX (746.5) was higher than for patients on RT (710.0).
Ivonava et al. (2005) To develop and validate a Russian-language version of the MDASI-R	n=226 inpatients and outpatients Age: 61 years (range: 18-92) Female: 62% Ethnicity: 100% Russian Various cancers Stage: 87% stage lll-lV Treatment: 40% CTX, 38% RT, 15% surgery	Cross-sectional MDASI SF-36	Most prevalent moderate to severe symptoms were fatigue (94%), sleep disturbances (59%), pain (53%), sadness (35%), and poor appetite (24%). 53% of the sample reported one to four symptoms at moderate to severe levels. 22% of the sample had five or more moderate to severe symptoms. Of those who reported severe symptoms, 48% reported at least one symptom and 37% reported one to three symptoms. Fatigue, pain, and sleep disturbance were prevalent symptoms in patients with solid tumors and hematologic malignancies. The prevalence rates for poor appetite, distress, and sadness were significantly greater in patients with solid tumors compared to hematologic malignancies. SOB and difficulty remembering were more common in patients with hematologic cancers. Patients on CTX reported more severe fatigue, SOB, difficulty remembering, drowsiness, and poor appetite than those who received RT. Symptoms interfered most with work and general activity followed by mood, enjoyment of life, and walking.

Author Purpose	Sample Characteristics	Design Instruments	Major Findings
Lobchuk et al. (1997) To describe differences between family caregivers' interpretations of symptom distress and patients' perceptions of symptom distress	n=41 Age: 65 years (range: 40-80) Female: 32% Ethnicity: Canadian Lung cancer Stage: 74% stage lll-lV Treatment: 29% CTX, 10% RT	Cross-sectional SDS MMSE KPS	Most distressing symptoms for patients were fatigue (65%), cough (57%), shortness of breath (42%), pain frequency (31%), poorer outlook (30%), and insomnia (30%). Most distressing symptoms for family caregivers were fatigue (70%), poorer outlook (55%), cough (55%), insomnia (45%), and frequent pain (40%). The average global SDS score for patients was 27.8 and for family caregivers was 31.3. Family caregivers tended to rate the patients' degree of distress as slightly more severe than the patients for all symptoms except difficulty with concentration.
Lobchuk & Degner (2002) To compare patient and family caregiver perceptual congruence on symptom experience	n=98 outpatients Age: 64.7 years (range: 35-86) Female: 61% Ethnicity: Canadian Various cancers Treatment: 42% CTX, 10% RT, and 51% none	Cross-sectional MSAS	Mean number of patient reported symptoms was 11.4. Mean number of family caregiver reported symptoms was 14.1. Both patients and family caregivers reported that the most highly prevalent physical symptoms were lack of energy, pain, and feeling drowsy. Worrying was the most prevalent psychological symptom. Most frequently occurring, severe, and distressing symptom as reported by both patients and family caregivers was lack of energy. Family caregivers tended to over-report symptom distress. Patient and family caregiver reports of physical symptoms were more highly correlated than their reports of psychological symptoms.

Author Purpose	Sample Characteristics	Design Instruments	Major Findings
Okuyama et al. (2003) To examine the validity and reliability of the Japanese version of the MDASI	n=252 outpatients Age: 62.5 years Female: 42% Ethnicity: 100% Japanese Various cancers Stage: 50% metastasis Treatment: 22% CTX, 2% RT	Cross-sectional MDASI EORTC POMS	Most common symptoms at the moderate to severe level were fatigue (36%), drowsiness (33%), distress (31%), dry mouth (29%), and disturbed sleep (26%). Over 30% of the patients experienced 3 symptoms at moderate or severe levels. The two symptoms that contributed the most to symptom interference were fatigue and sadness.
Portenoy, Kornblith, et al. (1994) To evaluate the prevalence, characteristics, and impact of pain and other symptoms in patients with ovarian cancer	n=151 inpatients and outpatients Age: 54 years (range: 23-86) Female: 100% Ethnicity: 92% white Ovarian cancer Stage: 82% stage lll-lV Treatment: 87% CTX	Cross-sectional MSAS Comprehensive pain questionnaire Rand Mental Health Inventory FLIC KPS	Mean number of symptoms per patient was 10.2. Inpatients experienced a mean of 11.2 symptoms whereas outpatients experienced a mean of 7.4 symptoms. Most prevalent symptoms were pain (62%), lack of energy (68%), psychological distress (worrying =72%, feeling sad=64%, feeling nervous=62%), and insomnia (57%). Most severe symptoms were worrying, lack of energy, pain, feeling sad, and difficulty sleeping. Most frequent symptoms were lack of energy, worrying, pain, difficulty sleeping, and feeling nervous. Most distressing symptoms were lack of energy, worrying, pain, feeling sad, and difficulty sleeping. Most severe, frequent, and distressing symptoms were worrying, lack of energy, and pain.

Author Purpose	Sample Characteristics	Design Instruments	Major Findings
Portenoy, Thaler, et al. (1994) To evaluate the validity of the MSAS in a heterogeneous population of cancer patients	n=243 inpatients and outpatients Age: 55.5 years (range: 23-86) Female: 61% Ethnicity: no information Prostate, colon, breast, or ovarian cancer Stage: 28% local disease, 56% metastasis Treatment: no specific information	Cross-sectional MSAS Memorial Pain Assessment Card Revised Rand Mental Health Inventory FLIC SDS KPS	Mean number of symptoms was 11.5. Inpatients reported a mean of 13.5 symptoms, whereas outpatients reported a mean of 9.7. Most prevalent symptoms were lack of energy (74%), worrying (71%), feeling sad (65%), pain (64%), feeling nervous (61%), drowsiness (60%), dry mouth (54%), and difficulty sleeping (52%). No significant differences in overall symptom prevalence by age, gender, tumor type, or extent of disease. Proportion of patients who reported a high level of symptom distress was always lower than the proportion of patients who reported the symptom as severe or frequent. A higher number of symptoms was associated with more psychological distress (r= -0.37) and poorer quality of life (r= -0.67).
Sarna (1993) To explore and describe symptom distress and its correlates in women with lung cancer	n=69 Age: 61 years (range: 50-72) Gender:100% female Ethnicity: 86% white Lung cancer Stage: 68% limited disease, 32% distant disease Treatment: 43% CTX, 9% RT, 4% combination treatment	Cross-sectional SDS KPS CARES-SF	Most distressing symptoms were fatigue (57%), pain (29%), insomnia (25%), poor outlook (23%), and appetite disruption (19%). 61% of women experienced more than one distressing symptom. 41% of patients with fatigue experienced pain and 31% of patients with fatigue experienced insomnia. 23% of women reported four or more symptoms. Higher symptom distress was associated with lower QOL (r=0.72) and poorer functional status (r=0.71). Presence of respiratory disease, previous CTX, recurrent disease, and absence of previous surgery were associated with higher levels of symptom distress. Age, treatment status, and site of metastasis were not associated with a higher level of symptom distress.

Author Purpose	Sample Characteristics	Design Instruments	Major Findings
Tishelman, Degner, & Bryan (2000) To explore the differences between patients' perceived importance of symptoms and patients' rated symptom intensity	n=26 patients at T1, 15 patients at T2, and 8 patients at T3 Age: 66.9 (T1), 64.5 (T2), and 66.0 years (T3) Female: 50% Ethnicity:100% Swedish Lung cancer Stage: no information Treatment: no specific information	Longitudinal study Over three times (T1: after first contact with unit, then 1 (T2) and 2 months later (T3)) SDS Thurstone Scale	SDS score was 2.02 at T1, 1.9 at T2, and 2.0 at T3. Most distressing symptoms were fatigue (69%), poor outlook (54%), shortness of breath (50%), insomnia (46%), and frequent pain (40%). At T1, T2, and T3, shortness of breathing, pain, and insomnia were rated as severe. At T1, fatigue, poor outlook, and insomnia were the most severe symptoms, whereas poor outlook, shortness of breath, and pain were the most distressing symptoms. Patients weighted the importance of symptoms differently than they weighted their intensity.
Wang et al. (2004) To establish and validate a Chinese version of the MDASI To examine the severity of symptoms caused by the most common cancers in China	n=249 inpatients Age: 51 years (range: 18-77) Female: 54% Ethnicity: 100% Chinese Various cancers Stage: 50% stage III-IV Treatment: 35% CTX, 12% RT, 21% surgery, 22% combined treatment	Cross-sectional MDASI MOS 36-SF ECOG-PS	Most severe symptoms were fatigue, sleep disturbance, distress, pain, and poor appetite. About 40% of patients reported severe symptoms and at least 2 symptoms were severe. Fatigue and sleep disturbance were the most severe symptoms for patients with breast and lung cancer whereas fatigue and lack of appetite were the most severe symptoms for patients with GI cancer. At least 30% of patients with lung cancer reported 7 symptoms as being moderate to severe symptoms whereas those with GI and breast cancer reported 4 to 5 symptoms as severe. Fatigue, sadness, drowsiness, and lack of appetite were significant predictors of and accounted for 49% of the variance in interference. The highest level of symptom interference was for work, enjoyment of life, and mood.

Author Purpose	Sample Characteristics	Design Instruments	Major Findings
Wang et al. (2006) To test the validity and reliability of a Filipino version of the MDASI To examine the prevalence and severity of cancer symptoms and their impact on Filipino patients' daily functioning	n=206 inpatients and outpatients Age: 47 years (range: 18-76) Female: 68% Ethnicity: 100% Filipino Various cancers Stage: 65% stage III-IV, 18% Metastasis Treatment: 32% CTX, 28% RT, 29% surgery	Cross-sectional MDASI	The top five moderate to severe symptoms were problem with remembering (43%), fatigue (40%), drowsiness (35%), sadness (31%), and numbness (31%). 62% of patients rated a single or multiple symptoms as severe. 44% of patients rated at least two symptoms as severe. Fatigue, sadness, distress, and pain were significant predictors of symptom interference.
Yan & Sellick (2004) To describe symptoms, psychological distress, social support, and quality of life of Chinese patients with newly diagnosed gastrointestinal cancer	n=146 outpatients Age: 55 years (range: 17-93) Female: 24% Ethnicity: 100% Chinese Esophagus, stomach, liver, pancreas, and colorectal cancer Stage: no information Treatment: 56% surgery, 14% CTX, 16% RT	Cross-sectional MSAS SAI BDI-SF SSQ CARES-SF (HRQoL) VAS (GQoL)	The mean number of symptoms was 5. The most prevalent symptoms were fatigue (63%), pain (42%), weight loss (41%), dry mouth (38%), and lack of appetite (36%). The most frequent symptoms were fatigue, vomiting, shortness of breath, lack of appetite, nausea, and pain. The most severe symptoms were change in the way food tastes, insomnia, hair loss, fatigue, and weight loss. The most distressing symptoms were insomnia, change in the way food tastes, hair loss, fatigue, and shortness of breath. Patients over 70 years of age and with liver cancer reported more symptom distress. Patients younger than 40 years of age had higher depression and anxiety than those 70 years of age or older. Depression (29%) and symptom distress (12%) accounted for the largest amount of variance HRQOL.

Abbreviations: BDI-SF: Beck Depression Inventory-Short Form, CARE-SF: Cancer Rehabilitation Evaluation System-Short Form, CTX: Chemotherapy, ECOG-PS: Eastern Cooperative Oncology Group Performance Status, EORTC: European Organization for-Research and Treatment of Cancer, FLIC: Functional Living Index Cancer, GI: Gastrointestinal, HRQOL: Health Related Quality of Life, KPS: Karnofsky Performance Status Scale, MDASI: M. D. Anderson Symptom Inventory, MMSE: Mini-Mental State Examination, MSAS: Memorial Symptom Assessment Scale, MOS 36-SF: Medical Outcome Survey-Short Form, POMS: Profile of Mood States, RT: Radiation Therapy, SAI: Spielberger State Anxiety Inventory, SDS: Symptom Distress Scale, SF-36: Short Form Health Survey, SOB: Shortness of Breath, SRQ: Symptom Representation Questionnaire, SSQ: Social Support Questionnaire, VAS: Visual Analogue Scale.

Table. 2. Characteristics and Psychometric Properties of Instruments Used to Measure Multiple Symptoms in Adults with Cancer

Instrument	Number of items and dimensions measured	Dimensions	Scale	Reliability	Validity	Number of studies
MDASI	13 symptoms severity items 6 interference items -Severity -Level of interference with function	Physical Psychological	11-point numeric rating scale Intensity = 0 (not present) to 10 (as bad as you can imagine) Interference = 0 (does not interfere) to 10 (interferes completely)	Internal consistency (Cronbach alpha= 0.82-0.91)	Content Construct	7
MSAS	32 items -Frequency -Severity -Distress	Physical Psychological	4- and 5-point Likert scales Severity and frequency = 1 (slight/rarely) to 4 (very severe/almost constantly) Distress = 0 (not at all) to 4 (very much)	Internal consistency (Cronbach alpha = 0.83-0.85)	Content Construct	5
SDS	13 items -Distress	Physical Psychological	5-point Likert scales Distress = 1 (the least amount of distress) to 5 (extreme distress)	Internal consistency (Cronbach alpha = 0.82) Test-retest	Criterion Content Construct	6

Abbreviations: MDASI=M.D. Anderson Symptom Inventory, MSAS=Memorial Symptom Assessment Scale, SDS=Symptom Distress Scale

Table 3. Comparison of the Symptoms Evaluated Using Three Multiple Item Symptom Instruments

M.D. Anderson Symptom Inventory **13 symptoms**	Memorial Symptom Assessment Scale **32 symptoms**	Symptom Distress Scale **13 symptoms**
Physical symptoms		
Pain	**Pain**	**Pain severity/frequency**
Fatigue	**Lack of energy**	**Fatigue**
Disturbed sleep	**Difficulty sleeping**	**Insomnia**
Dry mouth	Dry mouth	
	Mouth sores	
	Change in the way food tastes	
	Difficulty of swallowing	
Lack of appetite	**Lack of appetite**	**Lack of appetite**
	Weight loss	
Nausea	**Nausea**	**Nausea severity/frequency**
Vomiting	Vomiting	
		Bowel dysfunction
	Diarrhea	
	Constipation	
Drowsy (sleepy)	Feeling drowsy	
Shortness of breath	**Shortness of breath**	**Shortness of breath**
	Cough	Coughing
	Feeling bloated	
Numbness or tingling	Numbness/tingling in hands or feet	
	Itching	
	Dizziness	
		Poor activity
	Hair loss	
	Problem with sexual interest or activity	
	Problems with urination	
	Sweats	
	Swelling of arms or legs	
	Changes in skin	
Psychological symptoms		
Problem with remembering things	**Difficulty concentrating**	**Difficulty with concentration**
Feeling sad	**Feeling sad**	**Mood**
	Worrying	
	Feeling nervous	
	Feeling irritable	
Distress (upset)		
	"I don't look like myself"	Altered appearance
		Poor outlook

Table 4. Prevalence Rates for Physical and Psychological Symptoms Across the Various Studies

Physical Symptoms	**Holmes (1991)** **N=51 patients** **43% chemotherapy, 57% RT** ***SDS-11 symptoms***	**Sarna (1993)** **N=69 women with lung cancer** **43% chemotherapy** ***SDS***	**Degner &Sloan (1995)** **N=434 newly lung cancer** **34%chemotherapy, 63%RT** ***SDS***	**Lobchuk et al. (1997)** **N=37 with lung cancer** **29%chemotherapy, 10% RT** ***SDS***	**Tishelman & Degner (2000)** **N=26 patients with lung cancer** ***SDS***
Pain severity[1] and frequency[1] Pain [2,3]	37.3%	17.4% (S)/28.8 (F)	18.7% (S)/23.5% (F)	28% (S)/32% (F)	30.8%(S)/40% (F)
Fatigue or Tiredness[1,2] Lack of energy[3]	58.8% (T)	56.5%	38.9%	70%	69.2%
Insomnia[1] Difficulty sleeping[2,3]	23.5%	24.6%	30.9%	31%	46.2%
Dry mouth[2,3]					
Sore mouth[3]					
Taste change[3]					
Lack of appetite[1,2,3]	33.3%	18.8%	18%	29%	34.6%
Weight loss[3]					
Nausea severity[1]and frequency[1] Nausea[2,3]	13.7%	13% (S)/10.1%(F)	12.2%(S)/7.4%(F)	20% (S) /20% (F)	
Vomiting[2,3]					
Bowel dysfunction[1]	29.4%	8.6%	18.4%	25%	23.1%
Diarrhea[3]	9.8%				
Constipation[1]	29.4%				
Drowsiness[2,3]					
SOB[1,2,3]		15.9%	9%	41%	50%
Coughing[1,3]		17.4 %	13.4%	58%	26.9%
Feeling bloated[3]					
Numbness/Tingling[2,3]					
Itching[3]					
Dizziness[3]					
Psychological Symptoms					
Concentration[1,2,3]	43.1%		9.7%	21%	
Feeling sad[2,3]/Mood[1]	43.1%				
Worrying[3]					
Feeling nervous[3]					
Feeling irritable[3]					
Distress[2,3]					
Altered appearance[1]	50.9%	10.1%	19.6%	28%	34.6%
Poor outlook[1]		23.1%	23.5%	31%	53.8%

Physical Symptoms	**Cooley et al. (2003) N=117 with lung cancer 7%chemotherapy, 11%RT, & 38%surgery** ***SDS***	**Cleeland et al.(2000) N=527 with various cancer 56%chemotherapy, 23%biotherapy** ***MDASI***	**Okuyama et al. (2003) N=252 with various cancer 22%chemotherapy, 2%RT, & 2% surgery** ***MDASI***	**Wong et al. (2004) N=51 with lung cancer 35% chemotherapy 12% RT, 21% surgery** ***MDASI***	**Ivanova et al. (2005) N=226 with various cancer 40% chemotherapy, 38% RT, 15% surgery** ***MDASI***
Pain severity[1] and frequency[1] Pain [2,3]	37% (S)/56% (F)	34%	23%	25%	53%
Fatigue or Tiredness[1,2] Lack of energy[3]	64%	59%	36%	38%	90%
Insomnia[1] Difficulty sleeping[2,3]	49%	41%	26%	33%	81%
Dry mouth[2,3]		37%	29%	16%	22%
Sore mouth[3]		15%			
Taste change[3]					
Lack of appetite[1,2,3]	43%	39%	27%	22%	24%
Weight loss[3]				14%	
Nausea severity[1]and frequency[1] Nausea[2,3]		19%	13%	7%	9%
Vomiting[2,3]		11%	15%		1%
Bowel dysfunction[1]					
Diarrhea[3]		14%			
Constipation[1]		32%		12%	
Drowsiness[2,3]		41%	33		18%
SOB[1,2,3]		26%	23%	22%	17%
Coughing[1,3]		18%			
Feeling bloated[3]		23%		9%	
Numbness/Tingling[2,3]		29%	24%		11%
Itching[3]					
Dizziness[3]					
Psychological symptoms					
Concentration[1,2,3]		23%	15%	7%	15%
Feeling sad[2,3]/Mood[1]		32%	29%	17%	35%
Worrying[3]		43%			
Feeling nervous[3]		34%			
Feeling irritable[3]		33%			
Distress[2,3]		42%	31%	20%	9%
Altered appearance[1]					
Poor outlook[1]					

Physical Symptoms	**Donovan et al (2005) N=279 women with ovarian cancer 57% chemotherapy, 10%RT *MDASI***	**Chen & Tseng (2006) N-=151 with various cancer 50% chemotherapy *MDASI***	**Wang et al. (2006) N=206 with various cancer 32%chemotherapy *MDASI***	**Portenoy et al. (1994) N=151 with ovarian cancer 87% chemotherapy *MSAS***	**Portenoy et al. (1994) N=243 with various cancer *MSAS***
Pain severity[1] and frequency[1] Pain [2,3]	27%	72.8%	30.0%	61.8%	64.0%
Fatigue or Tiredness[1,2] Lack of energy[3]	59%	82.1%	40.0%	68.6%	73.7%
Insomnia[1] Difficulty sleeping[2,3]	14%	72.2%	27.0%	57.3%	52.3%
Dry mouth[2,3]		84.1%	29.0%	45.6%	54.4%
Sore mouth[3]				8.1%	12.4%
Taste change[3]				25.7%	35.4%
Lack of appetite[1,2,3]	2%	76.2%	26.0%	28.4%	44.4%
Weight loss[3]	2%			18.5%	27.1%
Nausea severity[1]and frequency[1] Nausea[2,3]	9%	52.3%	20.4%	35.6%	44.2%
Vomiting[2,3]	4%	45.0%	5.8%	13.3%	20.6%
Bowel dysfunction[1]	37%			28.6%	34.7%
Diarrhea[3]				20.8%	23.5%
Constipation[1]				28.6%	34.7%
Drowsiness[2,3]	5%	65.6%	35.4%	45.3%	59.8%
SOB[1,2,3]	7%	44.4%	14.1%	18.7%	23.5%
Coughing[1,3]				25.3%	28.6%
Feeling bloated[3]	25%			34.7%	37.2%
Numbness/Tingling[2,3]	26%	49.0%	30.6%	42.7%	37.2%
Itching[3]				22.3%	27.1%
Dizziness[3]	0%			16.2%	23.6%
Psychological symptoms					
Concentration[1,2,3]	4%	55.0%	43.2%	34.7%	40.5%
Feeling sad[2,3]/Mood[1]	9%	60.9%	31.0%	63.8%	65.0%
Worrying[3]				71.7%	70.7%
Feeling nervous[3]				61.5%	61.3%
Feeling irritable[3]				45.9%	47.0%
Distress[2,3]		72.2%	21.8%		
Altered appearance[1]					
Poor outlook[1]					

Physical Symptoms	**Chang et al. (2000) N=240 with various cancer No treatment information *MSAS***	**Lobchuk & Degner (2002) N=98 with various cancer 42% chemotherapy, 10% RT *MSAS***	**Yan & Sellick (2004) N=146 newly diagnosed GIT cancer 56% surgery, 14% chemotherapy, 16% RT *MSAS***	***Mean prevalence rate for each symptom across the 18 studies***
Pain severity[1] and frequency[1] Pain [2,3]	59%	51%	42%	***40% (S)/36% (F)***
Fatigue or Tiredness[1,2] Lack of energy[3]	62%	60.2%	63%	***62%***
Insomnia[1] Difficulty sleeping[2,3]	45%	39.2%	25%	***41%***
Dry mouth[2,3]	54%	37.8%	38.4%	***42%***
Sore mouth[3]		10.2%		***11%***
Taste change[3]		18.4%	11.6%	***23%***
Lack of appetite[1,2,3]	29%	36.7%	35.6%	***32%***
Wt loss[3]	33%	10.2%	42%	***22%***
Nausea severity[1]and frequency[1] Nausea[2,3]		19.4%	17.1%	***21% (S)/13% (F)***
Vomiting[2,3]		9.2%	11%	***13%***
Bowel dysfunction[1]		21.4%	15.1%	***24%***
Diarrhea[3]		11.2%	19.2%	***16%***
Constipation[1]		21.4%	15.1%	***27%***
Drowsiness[2,3]	44%	49.9%	13.7%	***36%***
SOB[1,2,3]	50%	29.6%/	15.8%	***26%***
Coughing[1,3]	33%	25.5%	15.8%	***26%***
Feeling bloated[3]		24.5%		***29%***
Numbness/Tingling[2,3]		26.5%		***29%***
Itching[3]		22.4%	18.5%	***23%***
Dizziness[3]		10.2%	29.5%	***20%***
Psychological symptoms				
Concentration[1,2,3]		15.3%		***25%***
Feeling sad[2,3]/Mood[1]		35.7%		***39%***
Worrying[3]	40%	41.8%		***54%***
Feeling nervous[3]	37%	29.6%		***45%***
Feeling irritable[3]	28%	33.7%		***37%***
Distress[2,3]				***34%***
Altered appearance[1]				***29%***
Poor outlook[1]				***33%***

Abbreviations: F: frequency, GIT: gastro-intestinal, MDASI[2]- M.D. Anderson Symptom Inventory, MSAS[3]- Memorial Symptom Assessment Scale, RT: radiation therapy, S: severity, SDS[1]- Symptom Distress Scale, SOB: shortness of breath

Differences in Symptom Clusters Identified Using Occurrence Rates Versus Symptom Severity Ratings in Patients At the End of Radiation Therapy

Jung-Eun Esther Kim, RN, MS, PhD(c)[1]

Marylin J. Dodd, RN, PhD, FAAN[1]

Bradley E. Aouizerat, PhD[1]

Thierry Jahan, MD[2]

Christine Miaskowski, RN, PhD, FAAN[1]

[1]Schools of Nursing and [2]Medicine

University of California, San Francisco

Abstract

The purposes of this study, in a sample of patients who underwent radiation therapy (RT) were: to identify the number and types of symptom clusters using the yes/no responses from the Memorial Symptom Assessment Scale (MSAS) at the end of RT; to identify the number and types of symptom clusters using the severity scores from the MSAS at the end of RT; to compare the identified symptom factor structures for the sample derived using the MSAS severity scores to those derived using the occurrence ratings; and to evaluate for differences in symptom factor severity scores between patients with breast and prostate cancer. Separate exploratory factor analyses (EFA) were performed to determine the number of symptom "factors" based on symptom occurrence rates and symptom severity ratings. Differences in severity scores for each of the symptom factors between patients with breast and prostate cancer were evaluated using the Mann-Whitney sample rank-sum test. While the specific symptoms within each symptom cluster were not identical, three very similar symptom factors (i.e., "mood-cognitive" symptom cluster, "sickness-behavior" symptom cluster, "treatment-related" symptom cluster) were identified regardless of whether occurrence rates or severity ratings were used to create the symptom clusters at the end of RT. However, the factor solution derived using the severity ratings fit the data better. Significant differences in all three symptom severity scores were found between patients with breast and prostate cancer. For all three symptom factors, the patients with breast cancer had higher symptom severity factor scores than the patients with prostate cancer.

Introduction

The clinical reality that oncology patients experience multiple symptoms as a result of their disease and its treatment fostered the need to do research on multiple symptoms and symptom clusters. In 2001, two papers in the oncology literature presented compelling evidence on the deleterious effects of symptom clusters on patient outcomes (Dodd, Miaskowski, & Paul, 2001; Given et al., 2001). In addition, as part of the National Institutes of Health (NIH) State of the Science Conference on Symptom Management in Cancer: Pain, Depression, and Fatigue (Patrick, Ferketich, et al., 2004), the concept of a symptom cluster was explored in terms of its occurrence, assessment, and treatment. This research, as well as the NIH conference, stimulated a series of studies on symptom clusters (for reviews see Barsevick, 2007; Miaskowski & Aouizerat, 2007).

To date, a variety of instruments and approaches have been used to assess multiple symptoms in oncology patients and to derive symptom clusters from these assessments. Of note, the three most commonly used instruments in these symptom cluster studies were the M. D. Anderson Symptom Inventory (MDASI, Cleeland et al., 2000), the Symptom Distress Scale (SDS; McCorkle and Young, 1978), and the Edmonton Symptom Assessment Scale (ESAS; Bruera, 1991). However, a comparison of the symptom clusters identified across the studies that used the MDASI (Cleeland et al., 2000; Chen & Tseng, 2006; Chen & Lin, 2007; Wang et al., 2007), the SDS (Sarna & Brecht, 1997), and the ESAS (Chow et al., 2007) is difficult for two reasons. First, the number of symptoms evaluated by these instruments ranges from 9 for the ESAS to 13 for the MDASI. In fact, only five symptoms (i.e., pain, fatigue, nausea, lack of appetite, shortness of breath) are common across all three instruments. Second, while the MDASI and the ESAS evaluate symptom severity, the SDS evaluates symptom distress.

Therefore, it is not surprising that inconsistent results are found across these six symptom cluster studies in terms of the number of clusters identified as well as the specific symptoms within each cluster.

Another factor that contributes to the difficulty in making comparisons of symptom clusters across studies is the heterogeneity of the samples that were evaluated in terms of cancer diagnoses, stage of disease, and cancer treatments. About half of the studies (Chen & Tseng, 2006; Chen & Lin, 2007; Chow, Fan, Hadi, & Filipczak, 2007; Cleeland, Mendoza, Wang, Chou, Harle, Morrissey et al., 2000; Wang et al., 2007) used heterogeneous samples, that ranged in age from 50 to 68 years. In these cross-sectional studies, the patients underwent a variety of cancer treatments and 24% to 100% had metastatic disease. In the studies that evaluated for symptom clusters in homogeneous samples, three assessed patients with lung cancer (Gift et al., 2003; Gift et al., 2004; Sarna & Bretch, 1997) and one focused on patients with brain tumors (Gleason, Case, Rapp, Ip, Naughton, Butler et al., 2007). However, even in these homogeneous samples, patients were at various stages of their disease and underwent different treatments. In addition, the instruments used to evaluate symptom clusters varied across these studies.

Finally, a variety of analytic procedures (i.e., factor analysis, cluster analysis, multiple dimensional scaling) were used to identify symptom clusters with both heterogeneous and homogeneous samples of patients in terms of their cancer diagnoses. The majority of the studies used factor analysis to derive between one and four symptom clusters (Chen & Lin, 2007; Chen & Tseng, 2006; Chow et al., 2007; Cleeland et al., 2000; Wang, Tsai, Chen, Lin, & Lin, 2007; Gift et al., 2003; Gift et al., 2004; Gleason et al., 2007; Sarna & Bretch, 1997). Of note, in the four studies that used the MDASI with heterogeneous samples (Chen & Tseng, 2006; Chen & Lin, 2007; Cleeland et al., 2000; Wang et al., 2007), two to three symptom clusters were derived

using factor analysis. While different symptom clusters or factors were reported across these four studies, they represent combinations of the following domains: a "general" symptom factor, a "gastrointestinal" symptom factor, and an "emotional" symptom factor. The commonality in the symptom factors across these four studies is encouraging and may be related to the use of the same instrument despite differences in patients' cancer diagnoses and treatments.

In contrast, in the three studies that evaluated symptom clusters in patients with lung cancer (Gift et al., 2003; Gift et al., 2004; Sarna & Bretch, 1997), while one to four symptom clusters were identified using factor analysis, commonalities in the clusters were not as evident. Differences in the number of clusters as well as differences in the composition of the clusters may be related to differences in the instruments used to assess the symptoms (i.e., SDS (McCorkle and Young, 1978) versus Physical Symptom Experience Scale (Given et al., 1993)), the number of symptoms assessed (i.e., 13 versus 37), or the dimensions of the symptom assessed (i.e., distress versus severity).

Because of the numerous methodologic differences across the studies of symptom clusters done to date, it is difficult to draw definitive conclusions regarding the number and types of symptom clusters that occur in oncology patients with a specific cancer diagnosis or in those who undergo a specific cancer treatment. In addition, it is interesting to note that none of the studies used the Memorial Symptom Assessment Scale (MSAS) to evaluate for symptom clusters. This omission is serious because the MSAS is the most comprehensive multidimensional symptom inventory (i.e., 32 symptoms) available with well established validity and reliability (Portenoy et al., 1994). Finally, as Miaskowski and colleagues noted (Miaskowski, Aouizerat, Dodd, & Cooper, 2007), studies are needed that compare the number and types of symptom clusters based on whether the symptom clusters are derived using ratings of symptom prevalence

(i.e., present or absent) or symptom severity. In addition, symptom cluster studies need to be done with homogeneous samples of patients in terms of cancer diagnosis and/or treatment.

Given the numerous methodological issues across the symptom cluster studies done to date, this study focused on a homogeneous sample of oncology patients in terms of cancer treatment (i.e., radiation therapy (RT)) and on a comparison of symptom clusters derived using occurrence and severity ratings. The specific purposes of this study, in a sample of oncology patients who underwent RT, were: 1) to identify the number and types of symptom clusters using the yes/no responses from the MSAS at the end of RT; 2) to identify the number and types of symptom clusters using the severity scores from the MSAS at the end of RT; 3) to compare the identified symptom factor structures for the sample derived using the MSAS severity scores to those derived using the occurrence ratings; and 4) to evaluate for differences in symptom factor severity scores between patients with breast and prostate cancer.

Methods

Participants and Settings

This study is part of a descriptive, longitudinal study that evaluated the trajectories of fatigue, pain, and sleep disturbances in oncology outpatients over the course of RT. Patients were included if they were: adults (> 18 years of age) who were able to read, write, and understand English; had a Karnofsky Performance Status (KPS) Score of $\geq$ 60; and were scheduled to received primary or adjuvant RT. Patients were excluded if they had metastatic disease; had more than one cancer diagnosis; or had a diagnosed sleep disorder. Patients were recruited from RT departments located in a Comprehensive Cancer Center and a community based oncology program. This study was approved by the Human Subjects Committee at the University of California, San Francisco and at the second study site.

Study Procedures

At the time of the simulation visit (i.e., approximately 1 week prior to the start of RT), patients were approached by a research nurse to discuss participation in the study. After obtaining written informed consent, they were asked to complete a number of baseline questionnaires and symptom inventories. Additional assessments were done over the course of RT and for four months after the completion of RT. Demographic and clinical data, as well as data from the MSAS (Portenoy, Thaler, Kornblith, Lepore, Friedlander-Klar, Coyle et al., 1994) that was completed at the end of RT were used in these analyses. Patients' medical records were reviewed for disease and treatment information.

Instruments

The demographic questionnaire provided information on age, gender, marital status, education, ethnicity, and employment status. In addition, patients completed a checklist of co-morbidities and the KPS scale (Karnofsky et al., 1948). The KPS is widely used to evaluate the functional status of cancer patients (Mor, Laliberte, Morris, & Wiemann, 1984) and has well established validity and reliability.

The MSAS is a valid and reliable self-report questionnaire designed to measure the multidimensional experience of symptoms (Portenoy et al., 1994). The MSAS contains a list of 32 physical and psychological symptoms that occur as a result of cancer or cancer treatment. Using the MSAS, patients were asked to indicate whether or not they had experienced each symptom in the past week. If they had experienced the symptom, they were asked to rate its severity, its frequency of occurrence, and its distress. The patients' responses to the symptom occurrence and severity items were used to create the symptom clusters. The reliability and

validity of the MSAS is well established (Portenoy et al., 1994; Chang, Hwang, Thaler, Kasimis, & Portenoy, 2004).

Data Analysis

All data analyses were done using SPSS Version 15 and MPlus version 5.0. Prior to the symptom cluster analyses, appropriate descriptive statistics were used to generate information on the patients' demographic and clinical characteristics, as well as symptom occurrence and severity.

Separate exploratory factor analyses (EFAs) were used to determine the number of symptom "factors" based on occurrence and severity ratings. Factor analysis is a generic term for several procedures that aim to identify whether correlations between a set of observed variables can be explained by a few latent, unobserved variables (i.e., factors) (Tabachnick & Fidell, 2001).

Symptom occurrence was measured as a dichotomous variable (i.e., present or absent). Symptom severity was measured using a 5-point Likert scale (i.e., 0=not at all, 1=mild, 2=moderate, 3=severe, 4=very severe). In order to have sufficient variation in the data to perform the EFAs, symptoms that were present in $\geq$ 20% of the patients, but not more than 80%, were used in these analyses.

The major decisions in factor analysis include how to estimate communality; how to determine the number of factors; and how to determine the method for rotating the factors to obtain the simple structure. For the dichotomous occurrence data, tetrachoric correlations were used to create the matrix of associations (Muthen, 1989). For the severity data, polychoric correlations were used to create the matrix of associations. For both of these EFAs, the sample structure was estimated using the method of unweighted least squares with promax (oblique)

rotation. The unweighted least squares estimator was chosen to achieve more reliable results because of the relatively small sample size (i.e., < 200) (Muthen, 1989).

Factor loadings were considered meaningful if they exceeded 0.30 (Thomson, 2002). The number of factors was considered sufficient to explain the symptom correlations if the model's Chi-Square was not significant and the root mean square error of approximation (RMSEA) was $\leq$ 0.06 (Muthen & Muthen, 2001). For each EFA, two, three, and four factor solutions were inspected.

Differences in severity scores for each of the symptom factors between patients with breast and prostate cancer were evaluated using the Mann-Whitney two sample rank-sum test. Differences were considered statistically significant at the $p < 0.05$ level.

Results

Demographic and Clinical Characteristics

As shown in Table 1, approximately 51% of the 160 patients in this study were male and 51% were married, with a mean age of 61.1 (SD=11.5) years. The majority of the patients were Caucasian (72.8%) and well educated (16.1 $\pm$ 2.9 years of education).

The clinical characteristics of the sample are summarized in Table 2. Over half of the patients had prostate cancer. Almost all of the breast cancer patients had undergone surgery prior to RT compared to only 9.8% of the patients with prostate cancer. The mean KPS score for the sample was 92.4 (SD=9.7), the mean number of comorbid conditions was 4.9 (SD=2.5), and the types of comorbid conditions were diverse.

Symptom Occurrence and Severity

The occurrence rates and severity scores for the 32 symptoms on the MSAS are summarized in Table 3. The thirteen symptoms that occurred in $\geq$ 20% of patients are bolded on

Table 3. The five symptoms that occurred most frequently were: lack of energy (59.4%), followed by pain (51.8%), difficulty sleeping (47.1%), feeling drowsy (44.4%), and sweats (39.9%). About 20% of the patients experienced 10 or more concurrent symptoms. Of the patients who had symptoms, the mean symptom severity scores ranged from 1.00 for hair loss to 2.58 for problems with sexual interest or activity. The five most severe symptoms were: problem with sexual interest or activity (2.58 $\pm$ 1.06), vomiting (2.50 $\pm$ 0.71), changes in skin (2.24 $\pm$ 0.83), swelling of arms or legs (2.10 $\pm$ 0.99), and difficulty sleeping (1.99 $\pm$ 0.80).

Symptom Clusters Based on Symptom Occurrence

As shown in Table 4, the EFA of the dichotomous ratings of symptom occurrence revealed three symptom factors. The three factor solution indicated a good fit between the data and the model ($\chi^2 = 46.3$, $p = 0.06$, RMSEA = 0.05) and each of the factors included at least three symptoms. However, the variance explained by each factor cannot be estimated with unweighted least squares. Of note, cough did not load on any factor.

An examination of the various symptoms within each factor was done to name the "symptom factors or "symptom clusters". The symptoms in factor 1 (i.e., difficulty concentrating, feeling sad, sweats, worrying, feeling irritable) were named the "mood-cognitive symptom cluster". The symptoms in factor 2 (i.e., pain, lack of energy, feeling drowsy) were named the "sickness behavior symptom cluster". Factor 3 included the symptoms of difficulty sleeping, no problem with urination, itching, and changes in skin. Therefore, it was named the "treatment-related symptom cluster". It should be noted that while the symptom on the MSAS was stated as "problem with urination", this symptom loaded negatively on the "treatment-related" symptom factor which indicates that patients who had a skin problem or itching had no problem with urination.

Symptom Clusters Based on Symptom Severity Ratings

As shown in Table 5, a three factor solution indicated a good fit between the data and the model ($\chi^2 = 27.9$, $p = 0.14$, RMSEA = 0.04) when symptom severity ratings were used in the EFA. The symptoms in Factor 1 (i.e., difficult concentrating, feeling sad, worrying, feeling irritable) were named the "mood-cognitive symptom cluster". The symptoms in Factor 2 (i.e., pain, lack of energy, feeling drowsy, difficulty sleeping) were named the "sickness behavior symptom cluster". The symptoms in Factor 3 (i.e., no problem with urination, itching, changes in skin) were named the "treatment-related symptom cluster". Of note, sweats did not load on any factor.

Comparison of the Factor Structures Derived from Ratings of Symptom Occurrence and Severity

Tables 4 and 5 summarize the symptom clusters derived from these two EFAs. For both EFAs, a three factor solution fit the data best. In addition, across the EFAs, the majority of the symptoms were contained within the same factors. However, in terms of the fit indices, the factor solution derived from the severity ratings ($\chi^2 = 27.9$, $p = 0.14$, RMSEA = 0.04) fit the data better than the factor solution derived from the occurrence ratings ($\chi^2 = 46.3$, $p = 0.06$, RMSEA = 0.05).

Evaluation of Differences in Symptom Factor Severity Scores Between Patients with Breast and Prostate Cancer

The correlations among the various symptoms within each symptom factor and the reliability estimates for each of the factor-based symptom indices based on symptom severity scores are presented in Table 6. For the "mood-cognitive" index, the item-total correlations ranged from 0.38 to 0.65 and its Cronbach's alpha was 0.81. For the "sickness-behavior" index, the item-total correlations ranged from 0.32 to 0.66 and its Cronbach's alpha was 0.72. In these

two symptom indicess, all of the symptoms within a factor were significantly correlated with each other, but not with the symptoms in the other factor.

In contrast, for the "treatment-related" index, the item-total correlations ranged from -0.11 to 0.42 and its' Cronbach's alpha was 0.48. In this factor, the correlations between problem with urination and itching, as well as changes in skin were negative at -0.13, and -0.23. However, the correlation between itching and changes in skin was significant and moderate at 0.42 ($p < 0.05$). These three symptoms were not correlated with symptoms in the other factors.

As shown in Table 7, significant differences in all three symptom severity scores were found between patients with breast and prostate cancer. For all three symptom factors, the patients with breast cancer had higher symptom severity factor scores than the patients with prostate cancer.

Discussion

To our knowledge, this study is the first to evaluate for differences in symptom clusters in a homogeneous sample of oncology patients who underwent RT using both the occurrence rates and severity ratings from the MSAS. While the specific symptoms within each factor were not identical, three very similar factors were identified regardless of whether occurrence rates or severity ratings were used in the factor analysis. However, because the factor solution derived using the severity ratings fit the data better, future studies of symptom clusters need to consider using this approach.

A comparison of the specific symptom factors identified in this study using symptom severity scores to previous reports that identified symptom clusters using severity or distress scores and factor analysis (Cleeland et al., 2000; Chen & Lin, 2007; Chen & Tseng, 2006; Chow et al., 2007; Gift et al., 2003; Gift et al., 2004; Gleason et al., 2007; Sarna & Bretch, 1997; Wang

et al., 2008) revealed some similarities as well as some distinct differences. Across the four studies of heterogeneous samples that used either the MDASI (Cleeland et al., 2000; Chen & Lin, 2007; Chen & Tseng, 2006) or the ESAS (Chow et al., 2007), a "sickness-behavior" symptom cluster was identified that included pain, fatigue, drowsiness, and sleep disturbance. However, this symptom cluster was not clearly identified in the symptom cluster studies of more homogeneous samples of patients with lung cancer (Gift et al., 2003; 2004; Wang et al., 2008) and brain tumor (Gleason et al., 2007). In contrast, only two of the previous studies of heterogeneous samples (Chen & Lin, 2007; Chen & Tseng, 2006) and one study of homogeneous sample of patients with brain tumor (Gleason et al., 2007) found a distinct mood-cognitive cluster.

The differences in the symptom clusters identified across studies may be related to differences in cancer diagnoses, cancer treatments, as well as the point in the patient's disease trajectory when symptoms were assessed. Another factor that may contribute to differences in symptoms contained within a cluster is the number as well as the specific symptoms on the symptom inventory. For example, on the MDASI only two symptoms (i.e., feeling sad and distress) evaluate psychological status, while on the MSAS, four symptoms (feeling sad, worrying, feeling nervous, feeling irritable) evaluate psychological status. Finally, the differences in the specific symptoms within a cluster may be due to whether severity (Cleeland et al., 2000; Chen & Lin, 2007; Chen & Tseng, 2006; Gift et al., 2003; Gift et al., 2004; Gleason et al., 2007; Wang et al., 2008) or distress (Chow et al., 2007; Sarna & Bretch, 1997) ratings were used in the factor analysis. Findings from this study as well as comparisons across studies suggest that the number and specific symptoms, as well as the rating scales, that are included on a multidimensional questionnaire need to be considered in future studies of symptom clusters.

This study is the first to identify a treatment-related symptom cluster that included the symptoms of lack of problem with urination, itching, and changes in skin. Clinical experience suggests that the problem with urination symptom would be more likely to occur in the men who underwent RT for prostate cancer and that the symptoms of itching and changes in skin would occur more frequently in the women who underwent RT for breast cancer. In fact, at the end of RT, 70% of the men reported a problem with urination compared to only 4.3% of the women ($\chi^2 = 64.74$, $p < 0.0001$). In contrast, 49% of the women reported itching and 43.1% reported changes in skin compared to only 17.1% ($\chi^2 = 16.64$, $p < 0.0001$) and 4.0% ($\chi^2 = 29.24$, $p < 0.0001$) of the men, respectively. This finding of a radiation treatment specific symptom cluster and perhaps within radiation treatments, a diagnosis specific radiation treatment-related symptom cluster warrants additional investigation. Due to sample size limitations within each diagnosis, separate factor analyses for breast and prostate cancer patients' symptom clusters could not be performed. However, this analysis needs to be done with larger samples. In fact, some support for the hypothesis that diagnosis specific treatment-related symptom clusters do exist comes from work by Gleason and colleges (2007) who found a language cluster in patients with brain tumors who underwent RT.

One symptom cluster that was not identified in this sample, but was identified in previous studies of heterogeneous samples of oncology patients (Chen & Tseng, 2006; Chen & Lin, 2007; Cleeland et al., 2000; Wang et al., 2007) is a gastrointestinal symptom cluster that included the symptoms of nausea and vomiting. While these symptoms are listed on the MSAS, they were reported by only 9% and 1% of this sample of patients. This finding suggests that this symptom cluster may occur more frequently in patients who receive CTX as noted in previous symptom cluster research (Chen & Tseng, 2006).

An interesting finding in this study is that women with breast cancer reported higher scores for all three of the factor-based symptom indicess. This finding is similar to previous studies that assessed for gender differences in the symptom experience (Akechi et al., 1999; Cooley, Short, & Moriarty, 2002; Degner & Sloan, 1995; Pater et al., 1997; Redeker et al., 2000). For example, Degner & Sloan (1995) and Cooley et al. (2002) found that women reported higher symptom distress scores than men. In addition, higher rates of depressive symptoms (de Leeuw et al., 2001; Hopwood et al., 2000) and higher fatigue severity scores (Akechi et al., 1999; Pater et al., 1997; Redeker et al., 2000) were found in women compared to men. However, others studies have failed to support these gender differences in the symptom experience of oncology patients (Ouellette and Kobasa, 1998; Kurtz et al., 2000; Portenoy et al., 1994; Walsh et al., 2000). Therefore, further research is needed on gender differences in the prevalence of, as well as the severity and distress associated with the symptoms of cancer and cancer treatment.

Several limitations of this study need to be mentioned. The sample size was relatively small and did not allow for separate evaluations of symptom clusters in patients with breast and prostate cancer. In addition, because only a single time point in the course of RT was assessed, the stability of symptom clusters over the course of RT was not evaluated. Future studies need to address these limitations.

Despite these limitations, findings from this study suggest that symptom clusters derived from ratings of severity rather than occurrence provide a more stable factor structure. In addition, future studies of symptom clusters need to consider an evaluation of homogeneous samples of patients in terms of both cancer diagnoses and treatments.

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Table 1. Demographic characteristics of the sample

Characteristic	**Mean (SD)**
Age (years)	61.1 (11.5)
Education (years)	16.1 (2.9)
	n (%)
Gender	
Female	78 (48.7)
Male	82 (51.3)
Ethnicity	
Caucasian-White	115 (72.8)
African American	25 (15.8)
Asian or Pacific islander	9 (5.7)
Hispanic	4 (2.5)
Other	5 (3.2)
Marital status	
Married/partnered	80 (51.0)
Separated or divorced	33 (21.0)
Never married	27 (17.2)
Widow or widower	9 (5.7)
Not married but living together	8 (5.1)
Employment status	
Employed	69 (44.5)
Unemployed	86 (55.5)

Table 2. Clinical characteristics of the sample

Characteristic	**Mean (SD)**
Mean number of comorbid conditions	4.9 (2.5)
Karnofsky Performance Status Score	92.4 (9.7)
Total dose of radiation administered (cGys)	6299.1 (1020.1)
	n (%)
Diagnosis	
Breast cancer	78 (48.7)
Prostate cancer	82 (51.3)
Previous cancer treatment	
Surgery	
Lumpectomy	57 (74.0%)
Partial mastectomy	9 (11.7%)
Simple mastectomy	4 (5.2%)
Prostatectomy	8 (9.8%)
Chemotherapy	43 (55.8%)
Hormonal therapy	74 (46.3%)
Five most common comorbid conditions	
Back problems	52.8%
Allergies	47.7%
Arthritis	35.5%
Headaches	32.5%
Hemorroids	14.4%

SD = standard deviation

Table 3. Symptom occurrence and severity

Symptoms	Occurrence %	Severity Mean (SD)
Lack of energy	**59.4**	1.96 (0.73)
Pain	**51.8**	1.83 (0.76)
Difficulty sleeping	**47.1**	1.99 (0.80)
Feeling drowsy	**44.4**	1.86 (0.68)
Sweats	**39.9**	1.97 (0.75)
Problems with urination	**37.1**	1.91 (0.76)
Difficulty concentrating	**35.9**	1.55 (0.69)
Feeling irritable	**34.0**	1.67 (0.71)
Itching	**31.9**	1.90 (0.78)
Worrying	**29.7**	1.89 (0.89)
Feeling sad	**26.9**	1.74 (0.79)
Cough	**22.3**	1.75 (0.76)
Changes in skin	**20.0**	2.24 (0.83)
Feeling nervous	18.4	1.68 (0.67)
Dry mouth	17.2	1.70 (0.70)
Numbness/tingling in hands/feet	16.5	1.80 (0.76)
Diarrhea	17.1	1.67 (0.64)
Problems with sexual interests or activity	15.7	2.58 (1.06)
Constipation	13.9	1.91 (0.75)
Dizziness	11.6	1.11 (0.32)
“I don’t look like myself”	12.1	1.75 (0.85)
Shortness of breath	9.6	1.60 (0.63)
Nausea	8.9	1.61 (0.65)
Lack of appetite	8.9	1.39 (0.51)
Feeling bloated	8.3	1.93 (0.73)
Weight loss	7.5	1.09 (0.30)
Swelling of arms or legs	5.6	2.10 (0.99)
Changes in the way food tastes	4.1	1.67 (0.82)
Mouth sores	3.4	1.33 (0.82)
Vomiting	1.4	2.50 (0.71)
Difficulty swallowing	1.4	1.50 (0.71)
Hair loss	0.7	1.00 (0.00)

* Symptoms in bold face type were included in the factor analyses

**Severity scores can range from 1 (mild) to 4 (very severe), SD = standard deviation

Table 4. Exploratory factor analysis using ratings of symptom occurrence

Symptoms	Factor I (Mood-cognitive symptom cluster)	Factor 2 (Sickness-behavior symptom cluster)	Factor 3 (Treatment-related symptom cluster)
Difficulty concentrating	**.53**		
Feeling sad	**.88**		
Sweats	**.36**		
Worrying	**.85**		
Feeling irritable	**.90**		
Pain		**.56**	
Lack of energy		**.77**	
Feeling drowsy		**.97**	
Difficulty sleeping			**.43**
Problem with urination			**-.76**
Itching			**.43**
Changes in skin			**.96**

Extraction method: unweighted least squares, Rotation method: promax (oblique) rotation

Table 5. Exploratory factor analysis using ratings of symptom severity

Symptoms	Factor I (Mood-cognitive symptom cluster)	Factor 2 (Sickness-behavior symptom cluster)	Factor 3 (Treatment-related symptom cluster)
Difficulty concentrating	**.49**		
Feeling sad	**.62**		
Worrying	**.94**		
Feeling irritable	**.81**		
Pain		**.50**	
Lack of energy		**.82**	
Feeling drowsy		**1.1**	
Difficulty sleeping		**.41**	
Problem with urination			**-.69**
Itching			**.36**
Changes in skin			**.91**

Extraction method: unweighted least squares, Rotation method: promax (oblique) rotation

Table 6. Polychoric correlations among symptoms within each symptom factor using ratings of symptom severity

Factor 1 – Mood-Cognitive Symptom Cluster				
	Difficulty concentrating	Feeling sad	Worrying	Feeling irritable
Difficulty concentrating	1			
Feeling sad	.57*	1		
Worrying	.55*	.65*	1	
Feeling irritable	.38*	.49*	.51*	1
Cronbach's alpha for Factor 1				.81
Factor 2 – Sickness behavior Symptom Cluster				
	Pain	Lack of energy	Feeling drowsy	Difficulty sleeping
Pain	1			
Lack of energy	.47*	1		
Feeling drowsy	.32*	.66*	1	
Difficulty sleeping	.44*	.33*	.34*	1
Cronbach's alpha for Factor 2				.72

Factor 3 – Treatment-related Symptom Cluster			
	Problem with urination	Itching	Changes in skin
Problem with urination	1		
Itching	-.13	1	
Changes in skin	-.23*	.42*	1
Cronbach's alpha for Factor 3			.48

* Correlation is significant at the 0.05 level (2-tailed).

Table 7. Differences in the mean symptom severity scores for the three symptom clusters between patients with breast and prostate cancer

Symptom Cluster Factors	Breast cancer M (SD)	Prostate cancer M (SD)	Z-value*	p-value
Mood-cognitive symptom cluster	.72 (.76)	.29 (.50)	-3.75	.000
Sickness-behavior symptom cluster	1.15 (.75)	.68 (.68)	-3.69	.000
Treatment-related symptom cluster	1.89 (.57)	1.01 (.36)	-7.48	.000

*Mann-Whitney U test
M = the mean symptom severity score
SD = Standard deviation

Changes in Symptom Clusters in Patients Undergoing Radiation Therapy

Jung-Eun Esther Kim, RN, MS, PhD(c)[1]

Marylin J. Dodd, RN, PhD, FAAN[1]

Bradley E. Aouizerat, PhD[1]

Thierry Jahan, MD[2]

Christine Miaskowski, RN, PhD, FAAN[1]

[1]Schools of Nursing and [2]Medicine

University of California, San Francisco

Abstract

The purposes of this study, in a sample of patients who underwent RT were: to determine the prevalence and severity of symptoms at the middle, end, and one month after the completion of RT; to determine the number and types of symptom clusters at these 3 time points; and to evaluate for changes over time in these symptom clusters. The specific symptoms used in each factor analysis were selected for each time point. At each time point (i.e., middle of RT, end of RT, 1 month after the completion of RT), an exploratory factor analysis (EFA) was performed to determine the number of symptom "factors" based on symptom severity ratings. Although the number and the specific symptoms within each symptom cluster were not identical across the three time points, three relatively similar symptom clusters (i.e., "mood-cognitive" symptom cluster, "sickness-behavior" symptom cluster, "treatment-related" or "pain" symptom cluster) were identified in this sample. The internal consistency coefficients for factor-based indices for "mood-cognitive" symptom cluster and "sickness-behavior" symptom cluster were adequate at > 0.70. Of note, the majority of the symptom cluster factor scores were significantly higher in patients with breast cancer compared to those with prostate cancer.

Introduction

Given the occurrence of multiple symptoms and their possible synergistic effects, the National Institutes of Health (NIH) (2004) suggested the need for studies on the assessment and management of symptom clusters. Because symptom cluster research is still in its infancy (NIH, 2004), a number of methodologic approaches (i.e., factor analysis, cluster analysis, correlations, multidimensional scaling) are being used to examine the correlations or "clustering" among symptoms. The majority of the research on symptom clusters is cross-sectional in nature and has evaluated heterogeneous sample of patients in terms of cancer diagnoses and treatments as well as at different time points in their disease and treatment trajectory (for reviews see Barsevick, 2007; Miaskowski & Aouizerat, 2007).

While findings from longitudinal studies of single symptoms suggest that the prevalence and severity of symptoms like fatigue change over the course of radiation therapy (RT) (Berger, 1998; Cooley et al., 2003; Irvine et al., 1998; Jacobsen et al., 1999; Smet et al., 1998), only seven studies have evaluated how symptom clusters change over the course of treatment (Ahlberg et al., 2005; Byar et al., 2006; Chan et al., 2005; Chow et al., 2007; Gift et al., 2003; Gleason et al., 2007; Wang et al., 2006). Among these studies, three reported no changes in symptom clusters (Gift et al., 2003; Gleason et al., 2007; Wang et al., 2006), while four found different patterns to the symptom clusters (Ahlberg et al., 2005; Byar et al., 2006; Chan et al., 2005; Chow et al., 2007). Almost 90% of the studies (n=6) were conducted using homogeneous samples of patients with either lung (Gift et al., 2003; Wang et al., 2006; Chan et al., 2005), uterine (Ahlberg et al., 2005), brain (Gleason et al., 2007), or breast (Byar et al., 2006) cancer. Patients in these studies were receiving active treatment with either chemotherapy (Byar et al., 2006), RT (Ahlberg et al.,

2005; Chan et al., 2005; Chow et al., 2007; Gleason et al., 2007), or both treatments (Gift et al., 2003; Wang et al., 2006).

The instruments used to measure the symptoms were highly variable. Three studies (Gift et al., 2003; Chow et al., 2007; Wang et al., 2006) used comprehensive symptom inventories (i.e., Symptom Checklist of 32 Symptoms, the Edmonton Symptom Assessment System (ESAS), M. D. Anderson Symptom Inventory (MDASI)) and evaluated symptom severity. The other four studies used symptom specific measures or symptom subscales from a quality of life (QOL) questionnaire (Ahlberg et al., 2005; Byar et al., 2006; Chan et al., 2005; Gleason et al., 2007).

Several analytic methods (i.e., correlations, factor analysis, cluster analysis, multidimensional scaling, mixed-effect growth curve models) were used to determine the symptom clusters. In three studies (Ahlberg et al., 2005; Byar et al., 2006; Chan et al., 2005), symptom clusters were determined by examining the magnitude of the correlations among the symptoms. These correlational analyses found that specific symptoms were moderately correlated with other symptoms over time.

In three studies (Chow et al., 2007; Gift et al., 2003; Gleason et al. 2007), factor analysis was used to identify symptom clusters. In one study of lung cancer patients (Gift et al., 2003), a single cluster of symptoms (i.e., nausea, fatigue, weakness, appetite loss, weight loss, altered taste, vomiting) was identified at diagnosis. This cluster of seven symptoms did not change at 3 and 6 months after diagnosis. However, the mean severity score for the symptom cluster decreased over time.

More recently, changes in symptom clusters in patients with bone metastasis were evaluated using 9 symptoms from the Edmonton Symptom Assessment Scale (ESAS) at five different time points during and after RT (Chow et al., 2007). Using factor analysis, three

symptom clusters (cluster 1 = fatigue, pain, drowsiness, poor sense of well-being; cluster 2 = anxiety, depression; cluster 3 = shortness of breath, nausea, poor appetite) were identified. Of note, specific symptoms in each of these symptom clusters changed over time. However, two symptoms in cluster 1 (i.e., fatigue, drowsiness) and two symptoms in cluster 2 (i.e., anxiety, depression) remained constant at all five time points.

In another longitudinal study of patients with brain tumors who underwent RT (Gleason et al., 2007), a variety of analyses (i.e., factor analysis, multidimensional scaling, cluster analysis) were used to identify symptom clusters based on patients' responses to three questionnaires (i.e., Functional Assessment of Cancer Therapy (FACT), the FACT-Brain subscale, the Center for Epidemiologic Studies Depression Scale (CESD)). Two symptom clusters (i.e., language, mood symptom clusters) were identified at the beginning of RT. No changes were found in the two symptom clusters during the course of RT. While, the symptom clusters identified using factor analysis were consistent with those found using multidimensional scaling and cluster analysis, data on changes in clusters over time were presented only for factor analysis.

Only three studies have evaluated for changes in symptom clusters over time and findings are inconsistent across these studies (Chow et al., 2007; Gift et al., 2003; Gleason et al. 2007). In addition, the majority of these studies had relatively small sample sizes and the symptom questionnaires were highly variable in terms of the number of symptoms and the dimension of the symptoms (i.e., occurrence, severity, distress) that were evaluated. Given the paucity of research on changes in symptom clusters over time, the purposes of this study, in a sample of patients who underwent RT were to determine the prevalence and severity of symptoms at the middle, end, and one month after the completion of RT; to determine the number and types of

symptom clusters at these 3 time points; and to evaluate for changes over time in these symptom clusters.

Methods

Participants and Settings

This study is part of a descriptive, longitudinal study that evaluated the trajectories of fatigue, pain, and sleep disturbances in oncology outpatients over the course of RT. Patients were included if they were: adults (> 18 years of age) who were able to read, write, and understand English; had a Karnofsky Performance Status (KPS) score of > 60; and were scheduled to receive primary or adjuvant RT. Patients were excluded if they had metastatic disease; had more than one cancer diagnosis; or had a diagnosed sleep disorder. Patients were recruited from RT departments located in a Comprehensive Cancer Center and a community based oncology program. This study was approved by the Human Subjects Committee at the University of California, San Francisco and at the second study site.

Study Procedures

At the time of the simulation visit (i.e., approximately 1 week prior to the start of RT), patients were approached by a research nurse to discuss participation in the study. After obtaining written informed consent, they were asked to complete a number of baseline questionnaires and symptom inventories. Additional assessments were done over the course of RT and for four months after the completion of RT. Demographic and clinical data, as well as data from the Memorial Symptom Assessment Scale (MSAS, Portenoy, Thaler, Kornblith, Lepore, Friedlander-Klar, Coyle et al., 1994) that was completed at the middle, end, and one month after the completion of RT were used in these analyses. Patients' medical records were reviewed for disease and treatment information.

Instruments

The demographic questionnaire provided information on age, gender, marital status, education, ethnicity, and employment status. In addition, patients completed a checklist of co-morbidities and the KPS scale (Karnofsky et al., 1948). The KPS is widely used to evaluate the functional status of cancer patients (Mor, Laliberte, Morris, & Wiemann, 1984) and has well established validity and reliability. In addition, the patients' medical records were reviewed for disease and treatment information.

The MSAS is a valid and reliable self-report questionnaire designed to measure the multidimensional experience of symptoms (Portenoy et al., 1994). The MSAS contains a list of 32 physical and psychological symptoms that occur as a result of cancer or cancer treatment. Using the MSAS, patients were asked to indicate whether or not they had experienced each symptom in the past week. If they had experienced the symptom, they were asked to rate its severity, its frequency of occurrence, and its distress. The patients' responses to severity items were used to create the symptom clusters at the three time points. The reliability and validity of the MSAS is well established (Portenoy et al., 1994; Chang, Hwang, Thaler, Kasimis, & Portenoy, 2004).

Data Analysis

All data analyses were done using SPSS Version 15 and MPlus version 5.0. Prior to the symptom cluster analyses, appropriate descriptive statistics were used to generate information on the patients' demographic and clinical characteristics, as well as on symptom occurrence and severity.

At each time point (i.e., middle of RT, end of RT, 1 month after the completion of RT), an exploratory factor analysis (EFA) was performed to determine the number of symptom

"factors" based on symptom severity ratings. Symptom severity was measured using a 5-point Likert scale (i.e., 0=not at all, 1=mild, 2=moderate, 3=severe, 4=very severe). In order to have a sufficient amount of data to perform the EFAs at each time point, symptoms that were present in $\geq$ 20% of the patients were used in these analyses. While this approach resulted in different numbers of symptoms being included in each EFA, it took into consideration the fact that as the patients progress through RT, the occurrence and severity of specific symptoms change over time. In addition, an occurrence of $\geq$ 20% was necessary to ensure a stable factor structure in relationship to the sample size for this study.

The major decisions in factor analysis include how to estimate communality; how to determine the number of factors; and how to determine the method for rotating the factors to obtain the simple structure. To create the matrix of associations between symptoms, polychoric correlations were used. The simple structure was estimated using the method of unweighted least squares with promax (oblique) rotation. The unweighted least squares estimator was chosen to achieve more reliable results because of the relatively small sample size (i.e., < 200 with ordinal items) (Muthen, 1989).

For each EFA, polychoric correlations were used to create the matrix of associations among 14 symptoms at Time 1 and among 12 symptoms at Times 2 and 3. Factor loadings were considered meaningful if they exceeded 0.30 (Thomson, 2002). The number of factors was considered sufficient to explain the symptom correlations if the model's Chi-Square was not significant and the root mean square error of approximation (RMSEA) was $\leq$ 0.08 (reference still pending). There are no firm guidelines for the interpretation for the RMSR, because the value is scale dependent with ULS estimation. However, the criterion was selected for the present data because it is consistent with RMSR estimate from analyses with similar date, for which the root

mean square error of approximation (RMSEA) indicated good or adequate fit. Further, a value of .08 or smaller for this relatively small data set indicates a relatively close correspondence between the residuals in the sample error matrix, and the residuals in the estimated error matrix for the population, on average. Similarities and differences among the symptom clusters found at Times 1, 2, and 3 were examined. However, no statistical analyses were performed because the best factor structures at each time point were different. For each time point, differences in severity scores for each of the symptom clusters between patients with breast and prostate cancer were evaluated using the Mann-Whitney two sample rank-sum test on factor-based indices (computed as the mean of the items). Differences were considered statistically significant at the $p < 0.05$ level.

Results

Patient and Treatment Characteristics

The demographic characteristics of the patients (n=160) at the time of the simulation visit are summarized in Table 1. The majority of the patients were male and married, with a mean age of 61.1 (SD=11.5) years. The majority of the patients were Caucasian (72.8%) and well educated (16.1 ± 2.9 years of education).

The clinical characteristics of the sample are summarized in Table 2. Over half of the patients had prostate cancer. Almost all of the breast cancer patients (90.9%) had undergone surgery prior to RT compared to only 9.8% of the patients with prostate cancer. The mean KPS score for the sample was 92.4 (SD=9.7), the mean number of comorbid conditions was 4.9 (SD=2.5), and the types of comorbid conditions were diverse.

Occurrence and Severity of Symptoms at Each Time Point

The occurrence rates for the symptoms that occurred in ≥ 20% of the patients at each time point are summarized in Table 3. Across all three time points, the most prevalent symptom was lack of energy, followed by pain, difficulty sleeping, feeling drowsy, and sweats. The least prevalent symptoms during and after RT were feeling nervous and numbness/tingling in hands/feet.

At the middle (Time 1) and end of RT (Time 2), lack of energy and pain were the most prevalent symptoms (> 50%), while lack of energy was the most common symptom (> 50%) in patients at one month after the completion of RT (Time 3). Overall about 20% of patients experienced 12 to 14 symptoms concurrently across all three time points.

The mean severity scores for each symptom at each time point are listed in Table 3. Symptom severity was analyzed by averaging the symptom severity scores for the patients who had the symptom. Lack of energy, difficulty sleeping, sweats, and problem with urination were the four most severe symptoms at all three time points.

Symptom Clusters at the Middle of RT (Time 1; n=152)

Fourteen symptoms were included in EFA with promax (oblique) rotation at Time 1. As shown in Table 4, a three factor solution indicated a good fit between the data and the model (RMSEA = 0.059). Five symptoms loaded on Factor 1: three psychological symptoms (i.e., feeling nervous, worrying, feeling irritable) and two skin symptoms (i.e., itching, changes in skin). Factor 1 was named the "mood-cognitive" symptom cluster. While skin problems associated with RT loaded on the first factor, these symptoms were not included in this symptom cluster because they were not related to the other symptoms in the cluster (i.e., correlations between the items itching and changes in skin and the other items in the cluster ranged from only

0.13 to 0.25). On the other hand, the three psychological symptoms within Factor 1 were moderately correlated with each other in the range of 0.49 to 0.59.

Factor 2 contained seven symptoms (i.e., difficulty concentrating, pain, lack of energy, feeling drowsy, difficulty sleeping, feeling sad, sweats) and was named the "sickness-behavior" symptom cluster. The third factor contained only two symptoms (i.e., diarrhea, problem with urination) and was named the "treatment-related" symptom cluster.

For the "mood-cognitive" factor-based symptom index, the item-total correlations ranged from 0.29 to 0.63 and its Cronbach's alpha was 0.70. For the "sickness-behavior" symptom index, the item-total correlations ranged from 0.30 to 0.73 and its Cronbach's alpha was 0.79. For the "treatment-related" symptom index, the item-total correlation was 0.47 and its Cronbach's alpha was 0.63. All of the symptoms in each of the symptom clusters were significantly correlated with each other, but not with the symptoms in the other factors.

Symptom Clusters at End of RT (Time 2; n=160)

Twelve symptoms were included in the EFA with promax (oblique) rotation at Time 2. It should be noted that cough did not load on any factors. As shown in Table 5, a three factor solution indicated a good fit between the data and the model ($\chi^2 = 27.9$, $p = 0.14$, RMSEA = 0.04). The four symptoms in Factor 1 (i.e., difficult concentrating, feeling sad, worrying, feeling irritable) were named the "mood-cognitive" symptom cluster. The five symptoms in Factor 2 (i.e., pain, lack of energy, feeling drowsy, difficulty sleeping, sweats) were named the "sickness-behavior" symptom cluster. The three symptoms in Factor 3 (i.e., problem with urination, itching, changes in skin) were named the "treatment-related" symptom cluster. For the "mood-cognitive" symptom index, the item-total correlations ranged from 0.38 to 0.65 and its Cronbach's alpha was 0.81. For the "sickness-behavior" symptom index, the item total

correlations ranged from 0.20 to 0.65 and its Cronbach's alpha was 0.72. In these two symptom indices, all of the symptoms within an index were significantly correlated with each other, but not with the symptoms in the other indices.

In contrast, for the "treatment-related" symptom cluster, the item-total correlation ranged from -0.13 to 0.42 and its' Cronbach's alpha was 0.48. In this factor, the correlations between problem with urination and itching as well as changes in skin were negative and relatively low at -0.13 and -0.23, respectively. However, the correlation between itching and changes in skin was moderate at 0.42. These symptoms were not correlated with symptoms in the other factors.

Symptom Clusters at 1 month After Completion of RT (Time 3; n=132)

For the one month follow-up, 12 symptoms were used in the EFA. As shown in Table 6, a three factor solution indicated a good fit between the data and the model (RMSEA = 0.056). Factor 1 included three symptoms (i.e., feeling nervous, problem with urination, feeling sad) and was named as "mood-cognitive" symptom cluster. Although problem with urination loaded on this factor, this symptom was not included in the symptom factor because it was not related to the other two symptoms. The corrrelations between problem with urination and feeling nervous and feeling sad were 0.13 and 0.15, respectively. The second factor consisted of six symptoms (i.e., difficulty concentrating, lack of energy, feeling drowsy, difficulty sleeping, worrying, feeling irritable) and was named the "sickness-behavior" symptom cluster. The third factor contained the symptoms of pain, numbness/tingling in hands/feet, and sweats and was named as "pain" symptom cluster.

For the "mood-cognitive" symptom index, the item-total correlations ranged from 0.16 to 0.42 and its Cronbach's alpha was 0.50. Problem with urination was reverse-scored to calculate the Cronbach's alpha since it loaded negatively. In Factor 1, the correlation between feeling

nervous and feeling sad was moderate (r = 0.52, p = .000). For the "sickness-behavior" symptom index, the item total correlations ranged from 0.40 to 0.57 and its Cronbach's alpha was 0.77. For the "pain" symptom index, the item-total correlations ranged from 0.27 to 0.40 and its Cronbach's alpha was 0.49. Similar to Factor 1, sweats was correlated weakly with pain and numbness/tingling in hands/feet (r = 0.16 and 0.28, respectively).

The Similarities and Dissimilarities in Symptom Clusters Across Time

The specific symptoms within each symptom cluster at the three time points are summarized in Table 7. Three distinct symptom clusters were found across the three time points: "mood-cognitive" symptom, "sickness-behavior" symptom, and "treatment-related" or "pain" symptom cluster. Although the number and specific symptoms within each cluster are not identical, similarities exist in the mood-cognitive and sickness-behavior symptom cluster. However, differences over time were noted in the "treatment-related" or "pain" symptom clusters. Specifically, at the middle of RT, problems with urination and diarrhea clustered together, while problem with urination and skin problems associated with treatment clustered together at the end of RT. Furthermore, a new symptom cluster of pain emerged at 1 month after completion of RT.

To evaluate the validity of the symptom clusters, differences in symptom factor-based scores, at each time point, between patients with breast and prostate cancer were calculated using the Mann-Whitney U-test. Score were computed as the mean of the items identified in the factor analysis. As shown in Table 8, at every time point and for every symptom cluster except the treatment-related symptom cluster at the middle of RT (i.e., problem with urination, diarrhea), the patients with breast cancer reported significantly higher symptom factor scores.

Discussion

To our knowledge, this study is the first to describe the occurrence rates and severity scores for the most common symptoms experienced by patients over the course of RT as well as changes over time in symptom clusters in these patients. Of note, lack of energy, pain, and difficulty sleeping were the most prevalent symptoms reported by patients at the middle, the end, and one month after the completion of RT. This finding is consistent with previous reports of fatigue in patients who underwent RT as well as chemotherapy (Bender et al., 2005; Chow et al., 2007; Wang et al., 2007). In addition, lack of energy, difficulty sleeping, sweats, and problem with urination were the most severe symptoms at all time points. However, while the occurrence of pain decreased over time, the severity of pain increased over time. Additional research is needed to determine the etiologies for the pain in these patients.

Another interesting finding is the relatively high occurrence of sweats, as well as its relatively high severity rating compared to other symptoms. Previous studies that used the MSAS reported that sweats occurred in 33.6% (Yan & Selick, 2004) to 40.0% (Portenoy et al., 1994) of patients with a severity rating of 1.67 (SD = 0.83) (Yan & Selick, 2004). The relatively high occurrence and severity of sweats in this sample may be associated with biologically or chemically induced menopause in both the patients with breast and prostate cancer. In fact, across the three measurement times, 24.3% to 32.1% of the men and 55.2% to 58.0% of women in this study reported sweats. This finding warrants additional investigation.

Although the number, as well as the specific symptoms within each symptom cluster were not identical across the three time points, three relatively similar symptom clusters (i.e., “mood-cognitive” symptom cluster, “sickness-behavior” symptom cluster, “treatment-related” or “pain” symptom cluster) were found over time. Of note, both the mood-cognitive symptom

cluster (Chow et al., 2007; Gleason et al., 2007) and the sickness-behavior symptom cluster (Chow et al., 2007; Wang et al., 2006) were found in other studies of patients who underwent to RT. For example, in a longitudinal study of patients with bone metastasis who underwent to RT (Chow et al., 2007), the symptoms of anxiety and depression clustered together over the course of RT (i.e., 5 measures). In addition, in a study of patients with brain tumors (Gleason et al., 2007), the symptoms of feeling nervous, feeling sad, and depressed mood formed a mood cluster at both the beginning and the end of RT.

The symptoms within the "sickness-behavior" symptom cluster found in this study were relatively stable over time. In fact, lack of energy, feeling drowsy, and difficulty sleeping were present at all three time points. The stability of these three symptoms is consistent with two previous longitudinal RT studies (Chow et al., 2007; Wang et al., 2006) and suggests that these symptoms require systematic assessment and management in patients who undergo RT. Of note, the internal consistency coefficients for this symptom cluster were consistently high across the three time points (i.e., Cronbach's alphas ranged from .71 to .79) in this study as well as in the study by Chow and colleagues (2007) (Cronbach's alphas ranged from .65 to .77).

A unique finding in this study is the "treatment-related" or "pain" symptom cluster that changed over time. At the middle of RT, the treatment-related symptom cluster consisted of the symptoms of diarrhea and problem with urination. Further examination of the data demonstrated that both of these symptoms occurred with a higher frequency in the patients with prostate cancer compared to those with breast cancer (i.e., problem with urination = 65.3% versus 5.6%; diarrhea = 40.5% versus 8.6%; $\chi^2 = 19.92$, $p < 0.0001$). At the end of RT, the treatment-related symptom cluster consisted of problem with urination, itching, and changes in skin. At this time point, 70% of the men reported a problem with urination compared to only 4.3% of women ($\chi^2 = 64.74$, $p <$

0.0001). In contrast, 49% of the women reported itching and 43.1% reported changes in skin compared to only 17.1% ($\chi^2 = 16.64$, $p < 0.0001$) and 4.0% ($\chi^2 = 29.24$, $p < 0.0001$) of the men, respectively. Finally, one month after the completion of RT, a new symptom cluster of pain, numbness/tingling in hands/feet, and sweats. All three of these symptoms occurred more frequently in the women with breast cancer than in the men with prostate cancer (i.e., pain = 50% versus 32.4%; $\chi^2 = 4.02$, $p = 0.045$; numbness/tingling = 32.7% versus 11.0%; $\chi^2 = 9.183$, $p = 0.002$; sweats = 53.6% versus 23.3%; $\chi^2 = 12.55$, $p < 0.0001$). Taken together, these findings suggest that future studies of symptom clusters in patients undergoing RT may need to be done within cancer diagnoses to better determine treatment-related symptom clusters.

Several limitations of this study need to be mentioned. The sample size was relatively small and did not allow for separate evaluations of symptom clusters in patients with breast and prostate cancer. In addition, as with other longitudinal studies, dropouts occur over time. Therefore, the sample size for each analysis was different. In addition, because the prevalence of the various symptoms changed overtime, different symptoms were entered into the various EFAs. Some of these limitations may be overcome with large samples of patients.

Despite these limitations, the findings from this study suggest that a “mood-cognitive” and a “sickness-behavior” symptom clusters occur in patients during the course of RT. These symptoms need to be assessed and managed in these patients. In addition, treatment-related symptom clusters that appear to be diagnosis specific warrant additional investigation in future studies.

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Table 1. Demographic characteristics of the sample

Characteristic	**Mean (SD)**
Age (years)	61.1 (11.5)
Education (years)	16.1 (2.9)
	n (%)
Gender	
Female	78 (48.7)
Male	82 (51.3)
Ethnicity	
Caucasian-White	115 (72.8)
African American	25 (15.8)
Asian or Pacific islander	9 (5.7)
Hispanic	4 (2.5)
Other	5 (3.2)
Marital status	
Married/partnered	80 (51.0)
Separated or divorced	33 (21.0)
Never married	27 (17.2)
Widow or widower	9 (5.7)
Not married but living together	8 (5.1)
Employment status	
Employed	69 (44.5)
Unemployed	86 (55.5)

Table 2. Clinical characteristics of the sample

Characteristic	**Mean (SD)**
Mean number of comorbid conditions	4.9 (2.5)
Karnofsky Performance Status Score	92.4 (9.7)
Total dose of radiation administered (cGys)	6299.1 (1020.1)
	n (%)
Diagnosis	
Breast cancer	78 (48.7)
Prostate cancer	82 (51.3)
Previous cancer treatment	
Surgery	
Lumpectomy	57 (74.0%)
Partial mastectomy	9 (11.7%)
Simple mastectomy	4 (5.2%)
Prostatectomy	8 (9.8%)
Chemotherapy	43 (55.8%)
Hormonal therapy	74 (46.3%)
Five most common comorbid conditions	
Back problems	52.8%
Allergies	47.7%
Arthritis	35.5%
Headaches	32.5%
Hemorroids	14.4%

SD = Standard deviation

Table 3. Occurrence and severity rates for symptoms at each time point

Symptoms	Middle of RT (n=152)		End of RT (n=160)		1 month after the completion of RT (n=132)	
	%	M (SD)	%	M (SD)	%	M (SD)
Lack of energy	**55.2**	**1.83 (0.66)**	**59.4**	**1.96 (0.73)**	**51.6**	**1.85 (0.69)**
Pain	**50.3**	1.78 (0.75)	**51.8**	1.83 (0.76)	**39.8**	**1.93 (0.64)**
Difficulty sleeping	**47.2**	**1.90 (0.83)**	**47.1**	**1.99 (0.80)**	**47.2**	**1.80 (0.85)**
Feeling drowsy	**51.0**	1.59 (0.59)	**44.4**	1.86 (0.68)	**44.7**	1.61 (0.67)
Sweats	**42.5**	**2.00 (0.75)**	**39.9**	**1.97 (0.75)**	**36.4**	**1.92 (0.81)**
Problems with urination	**35.7**	**1.96 (0.59)**	**37.1**	**1.91 (0.76)**	**35.4**	**1.84 (0.74)**
Difficulty concentrating	**38.1**	1.48 (0.64)	**35.9**	1.55 (0.69)	**31.3**	1.59 (0.72)
Feeling irritable	**34.7**	1.54 (0.61)	**34.0**	1.67 (0.71)	**37.1**	1.62 (0.64)
Itching	**27.0**	1.63 (0.58)	**31.9**	1.90 (0.78)	13.6	1.59 (0.71)
Worrying	**31.0**	1.74 (0.68)	**29.7**	1.89 (0.89)	**30.5**	1.74 (0.76)
Feeling sad	**29.9**	1.76 (0.86)	**26.9**	1.74 (0.79)	**29.8**	1.72 (0.66)
Cough	17.6	**1.81 (0.98)**	**22.3**	1.75 (0.76)	14.4	1.63 (0.60)
Changes in skin	**24.5**	1.67 (0.61)	**20.0**	**2.24 (0.83)**	12.2	1.65 (0.79)
Feeling nervous	**20.0**	1.72 (0.65)	18.4	1.68 (0.67)	**20.0**	1.70 (0.64)
Numbness/tingling in hands/feet	18.9	1.74 (0.63)	16.5	1.80 (0.76)	**20.3**	1.79 (0.57)
Diarrhea	**25.5**	1.76 (0.64)	17.1	1.67 (0.64)	9.1	1.36 (0.67)

SD= Standard deviation

Severity scores ranges from 1 (mild) to 4 (very severe)

Table 4. Factor structure at the middle of radiation therapy (N=152)

Symptoms	Factor I (Mood-cognitive symptom)	Factor 2 (Sickness-behavior symptom)	Factor 3 (Treatment-related symptom)
Feeling nervous	**.74**	.23	.12
Worrying	**.58**	.44	.01
Feeling irritable	**.62**	.25	.33
Itching	**.47**	-.03	-.19
Changes in skin	**.63**	.09	-.29
Difficulty concentrating	.47	**.59**	.03
Pain	-.06	**.49**	.05
Lack of energy	.24	**.73**	-.03
Feeling drowsy	.37	**.61**	.03
Difficulty sleeping	.18	**.56**	-.03
Feeling sad	.46	**.60**	-.01
Sweats	-.00	**.59**	-.18
Problems with urination	.03	-.04	**1.02**
Diarrhea	.04	.05	**.60**

Table 5. Factor structure at the end of radiation therapy (N=160)

Symptoms	Factor I (Mood-cognitive symptom)	Factor 2 (Sickness-behavior symptom)	Factor 3 (Treatment-related symptom)
Difficulty concentrating	**.49**	.31	.17
Feeling sad	**.62**	.30	.11
Worrying	**.94**	.03	-.05
Feeling irritable	**.81**	-.08	.04
Pain	-.12	**.50**	.33
Lack of energy	.02	**.82**	.11
Feeling drowsy	.06	**1.1**	-.50
Difficulty sleeping	.18	**.41**	.17
Problems with urination	.27	.15	**-.69**
Itching	.28	.09	**.36**
Changes in skin	.29	-.19	**.91**

Table 6. Factor Structure at 1 month after the completion of radiation therapy (n=132)

Symptoms	Factor I (Mood-cognitive symptom)	Factor 2 (Sickness-behavior symptom)	Factor 3 (Pain symptom)
Feeling nervous	**.57**	.52	-.05
Feeling sad	**.63**	.46	.01
Problems with urination	**-.38**	.16	-.14
Difficulty concentrating	.40	**.64**	-.05
Lack of energy	-.05	**.73**	.17
Feeling drowsy	-.07	**.90**	-.14
Difficulty sleeping	.05	**.44**	.07
Worrying	.56	**.64**	-.07
Feeling irritable	.16	**.71**	-.02
Pain	-.07	.05	**.49**
Numbness/tingling in hands/feet	.04	-.12	**1.05**
Sweats	.04	.33	**.39**

Table 7. Symptom clusters and reliability estimates across time points

	Middle of RT	End of RT	1 month after the completion of RT
Mood-cognitive Symptom Cluster	Feeling nervous Worrying Feeling irritable Itching Changes in skin	Difficulty concentrating Worrying Feeling irritable Feeling sad	Feeling nervous Problem with urination Feeling sad
Cronbach's alpha	.70	.81	.50
Sickness-behavior Symptom Cluster	Pain Lack of energy Feeling drowsy Difficulty sleeping Feeling sad Difficulty concentrating Sweats	Pain Lack of energy Feeling drowsy Difficulty sleeping Sweats	Worrying Lack of energy Feeling drowsy Difficulty sleeping Feeling irritable Difficulty concentrating
Cronbach's alpha	.79	.71	.77
Treatment-related or Pain Symptom cluster	Problems with urination Diarrhea	Problem with urination Itching Changes in skin	Pain Numbness/tingling in hands/feet Sweats
Cronbach's alpha	.63	.48	.49

Table 8. Differences in the mean symptom severity scores for the three symptom clusters between patients with breast and prostate cancer

Symptom Cluster	Patient Group	Middle of RT		End of RT		1 month after the completion of RT	
		M (SD)	p-value*	M (SD)	p-value*	M (SD)	p-value*
Mood-cognitive	Breast cancer	.65 (.53)	.000	.72 (.76)	.000	1.72 (.58)	.000
	Prostate cancer	.27 (.45)		.29 (.50)		1.11 (.42)	
Sickness-behavior	Breast cancer	.88 (.61)	.002	1.15 (.75)	.000	.77 (.62)	.004
	Prostate cancer	.55 (.55)		.68 (.68)		.41 (.46)	
Treatment-related or Pain	Breast cancer	.12 (.35)	.000	1.89 (.57)	.000	.82 (.74)	.000
	Prostate cancer	.97 (.83)		1.01 (.36)		.37 (.43)	

*Mann-Whitney U test
M = the mean symptom severity score
SD = Standard deviation

Conclusions and Recommendations for Future Research

The purposes of the studies presented in this dissertation were to identify the number and type of symptom clusters in patients with cancer undergoing RT and to determine whether symptom clusters changed during the course of RT. An examination of symptom clusters began because the clinical reality is that oncology patients present with multiple symptoms and a single symptom-oriented approach does not provide sufficient information about the patients who experience multiple symptoms (Dodd, Miaskowski, & Paul, 2001).

Since symptom clusters initially were defined as three or more concurrent symptom that are related to each other (Dodd et al., 2001), it was proposed that symptom clusters consist of at least two or more interrelated symptoms, are a stable group of symptoms, and are relatively independent of other clusters (Kim, McGuire, Tulman, & Barsevick, 2005). These definitions specify important characteristics of a symptom cluster such as relationships among symptoms, the co-occurrence of symptoms, and the tendency for stable groups of symptoms to occur together over time. However, the concept of a symptom cluster is not fully developed in terms of specific symptoms within a cluster and the stability of occurrence of specific symptoms in a cluster over the course of a patient's disease and treatment trajectory.

Based on the findings from this dissertation research, additional longitudinal research is warranted to establish specific criteria for inclusion of specific symptoms within a symptom cluster, as well as to explore the stability of symptom clusters over time. Studies are needed that evaluate for changes in symptom clusters over the course of a specific disease and treatment and whether changes in symptom clusters are influenced by various cancer diagnoses.

The present study identified symptom clusters in patients with cancer across the treatment trajectory of RT. Findings from this study provide preliminary evidence that some symptoms

within a cluster tended to co-occur across time. These findings provide preliminary information that can be used to educate patients about what to expect during and after cancer treatment and may assist clinicians to better assess and manage these co-occurring symptoms.

Recent discussions suggest that a common biologic basis for symptoms may exist that is mediated by the release of pro-inflammatory cytokines. This syndrome has been called cytokine-induced "sickness-behavior" (Cleeland, Bennett, Dantzer, Dougherty, Dunn, Meyers et al., 2003; Lee, Dantzer, Langley, Bennett, Dougherty, Dunn et al., 2004). Findings from the present study support the idea that two symptom clusters (i.e., "mood-cognitive" and "sickness behavior") may occur in patients with cancer. While a few researchers have proposed that symptoms may share a common mechanism (Cleeland, et al., 2003; Lee et al., 2004), these hypotheses are based on findings from animal models. Therefore, the need exists to further explore the common biologic basis for symptom clusters in oncology patients.

Future longitudinal studies need to use larger samples to discern whether the occurrence of symptom clusters are dependent on both the type of treatment and the patient's cancer diagnosis. These types of studies may lead to a better understanding of symptom clusters as well as to more effective and cancer diagnosis based interventions.

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