

OBJECTIVES:

To examine symptom clusters in oncology patients; to determine if these symptom clusters might share a common biologic mechanism; and to describe potential biologic mechanisms that warrant investigation.

DATA SOURCES:

Synthesis of the theoretical and research papers on symptom clusters.

CONCLUSION:

Definitive conclusions about whether there is a biologic basis for the clustering of symptoms cannot be determined at this time. The animal model of sickness behavior holds promise as a potential biologic mechanism for clustering symptoms.

IMPLICATIONS FOR NURSING PRACTICE:

Until more definitive studies of symptom clusters are performed, clinicians need to monitor patients for the co-occurrence of multiple symptoms and develop appropriate management plans.

KEY WORDS:

Symptom clusters, symptom assessment, cluster analysis, mechanisms

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IS THERE A BIOLOGICAL BASIS FOR THE CLUSTERING OF SYMPTOMS?

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PATIENTS with cancer rarely experience a single symptom as a result of their disease or its treatment. However, most symptom management studies have taken a reductionistic approach and focused on the assessment or management of a single symptom like pain, fatigue, depression, or nausea.¹⁻³ In 2001, Dodd et al³ suggested that symptom management research needed to focus on multiple symptoms that are related to each other but are not required to share the same etiology. However, this definition did not address the issue of whether or not the symptoms within a cluster could or needed to share a common biological mechanism.

The article by Dodd et al³ launched a series of studies⁴⁻¹² and conceptual reviews¹³⁻¹⁷ on a variety of symptom clusters in oncology. Within a concept analysis of symptom clusters, Kim et al¹⁴ extended the definition of a symptom cluster as follows: "A symptom cluster consists of two or more symptoms that are related to each other and that occur together. Symptom clusters are composed of stable groups of symptoms, are relatively independent of other clusters, and may reveal specific underlying dimensions of symptoms. Relationships among symptoms within a cluster should be stronger than relationships among symptoms across different clusters. Symptoms in a cluster may or may not share the same etiology."^{14, p278} Again, this expanded definition does not address the focus of this article, namely whether or not symptoms within a cluster could or should share a common biological mechanism.

The purposes of this article are: to examine the symptom clusters identified to date in oncology patients; to determine if these symptom clusters might share a common biologic mechanism; and to describe potential biologic mechanisms that might be investigated in subsequent research on cancer-related symptom

clusters. Although symptoms contained within a cluster may share a common etiology (eg, nausea, diarrhea, and anorexia may occur as a result of a gastrointestinal tumor or cancer chemotherapy), that does not mean they share a common biologic mechanism. The converse may be true as well: symptoms within a cluster that have different etiologies (eg, pain from bone metastasis, fatigue from radiation therapy, and depression from the loss of a spouse) may share a common biologic mechanism.

SIMILARITIES AND DIFFERENCES IN SYMPTOM CLUSTERS IN ONCOLOGY PATIENTS

The studies on symptom clusters in oncology patients can be categorized into two groups. In one group (summarized in Table 1),^{3,4,8} the investigators created an a priori cluster of symptoms and evaluated the impact of that symptom cluster on a patient outcome. In the second group (summarized in Table 2),^{4-12,18} oncology patients completed a symptom inventory and in some of these studies, symptom clusters were identified empirically using either cluster analysis or factor analysis procedures.

In the first group,^{3,4,8} pain and fatigue were the common symptoms across all three studies. In all but one of these studies,⁸ sleep disturbance was the third symptom in the cluster that was created a priori. In all three studies, the rationale for the a priori selection of these symptoms was that they are highly prevalent in oncology patients. However, none of these articles discussed the idea that these symptoms could share a common biologic mechanism.

Some of the studies listed in Table 2 used either cluster analysis or factor analysis procedures to empirically derive symptom clusters.^{6,10-12,18} This group of studies, which used analytic procedures to derive symptom clusters, has the potential to more easily identify symptoms that may share a common biologic mechanism because these statistical procedures examine the inter-relationships among variables and disentangles those relationships to identify clusters of variables that are closely linked.^{19,20}

Two of the studies enrolled patients with a single cancer diagnosis (ie, lung cancer⁶ or breast cancer¹⁰), while the other three studies enrolled inpatients with a variety of cancer diagnoses.^{11,12,18} It is interesting to note that in the two studies with samples from a single cancer

diagnosis,^{6,10} a single symptom cluster with six or seven symptoms was identified using either factor analysis or cluster analysis. The symptoms shared across the two studies were fatigue and weakness. Symptoms in the single cluster that were unique to the patients with lung cancer were nausea, vomiting, loss of appetite, weight loss, and altered taste sensations. Symptoms in the single cluster that were unique to the patients with breast cancer were lack of energy, feeling depressed or blue, feeling nervous or anxious, and loss of concentration. The differences in the specific symptoms within the single cluster solution may relate to differences in symptoms associated with specific cancers or cancer treatments or in the questionnaires and methods that were used to assess and create the symptom cluster. Bender et al¹⁰ noted in their discussion that additional studies are needed to identify the physiologic mechanisms that underlie these symptom clusters.

The three studies that enrolled patients with a variety of cancer diagnoses derived two,¹⁸ three,¹² or seven¹¹ symptom clusters. While the studies by Cleeland et al¹⁸ and Chen and Tseng¹² both used the M.D. Anderson Symptom Inventory and similar analytic methods, the symptom clusters identified in these studies were not identical. However, in both studies, within one symptom cluster, the symptoms of pain, fatigue, sleep disturbance, and drowsiness did overlap. In addition, in both studies, a gastrointestinal symptom cluster (ie, nausea and vomiting) was identified. In addition, the study by Walsh and Rybicki,¹¹ of palliative care patients (n = 922), identified a gastrointestinal symptom cluster with the same symptoms of nausea and vomiting. However, pain, fatigue, and sleep disturbance did not cluster together in their sample. Variations in the number of symptom clusters, as well as in the particular symptoms within each cluster, may be attributable to the instruments used to measure the symptoms, the methods used to create the symptom clusters, and/or the heterogeneous nature of the patients in terms of cancer diagnoses, stages of disease, and current treatment regimens.

The authors of the most recent studies (listed in Table 2)^{11,12} noted that further research is needed on symptom clusters because this work may promote our understanding of the etiology and pathophysiology of multiple symptoms in patients with cancer. Chen and Tseng¹² proposed that one potential mechanism to explain certain symptoms

Table 1.
Studies of Oncology Patients That A Priori Selected a Symptom Cluster

Study, Purpose, and Symptoms in the Cluster	Sample Characteristics	Major Findings
Dodd et al, 2001³ <u>Purpose:</u> To determine the effect of the symptom cluster of pain, fatigue, and sleep insufficiency on functional status during three cycles of CTX <u>Symptoms:</u> pain, fatigue, and sleep insufficiency	N = 93 patients Age = 55.4 years Education = 14.8 years Female = 72% Married/partnered = 65% White = 87% Cancer diagnosis = all types of cancer Treatment = CTX	• Change in functional status from the first cycle to the third cycle of CTX was explained by age, pain, fatigue, and sleep insufficiency • Intercorrelations among the three symptoms were small • Symptom clusters have an adverse effect on patient outcomes
Given et al, 2001⁸ <u>Purpose:</u> To examine the co-occurrence of symptoms and patterns of change among combinations of pain and fatigue, and a number of other symptoms reported by patients newly diagnosed with four types of cancer who were followed for 1 year <u>Symptoms:</u> pain, fatigue, and one or more of 20 other symptoms	N = 845 patients Age = 69% were 65-74 years; 31% were ≥ 75 years Female = 45% Cancer diagnosis = breast, colon, lung, or prostate Treatment = surgery, CTX, or RT	• No evidence was found that age, gender, comorbidity, or site of cancer interacted with one another to predict different combinations of pain and/or fatigue • When compared with early stage cancer, late stage was significant in differentiating those who reported both pain and fatigue from those who reported pain alone • Time since diagnosis had a significant effect, independent of cancer site, stage, or treatment modality on reports of pain and fatigue, such that as time since diagnosis progressed, patients were significantly more likely to report neither pain nor fatigue or to report only one of these symptoms when compared with reporting both • Patients with 3 or more comorbid conditions were more likely to report pain, fatigue, or their combinations • The presence of pain and fatigue were independent predictors of the numbers of other symptoms that patients reported • Mediation analyses indicated that pain influences fatigue directly as well as indirectly by its effect on sleep • About 20% of the variation in fatigue is explained by pain
Beck et al, 2005⁴ <u>Purposes:</u> To examine the relationships among three symptoms (pain, sleep disturbance, fatigue); to determine to what extent pain intensity affects sleep disturbance and fatigue; and to test whether sleep disturbance mediated the effect of pain on fatigue <u>Symptoms:</u> pain, fatigue, sleep disturbance	N = 84 patients Age = 54. years Female = 53% Married/partnered = 67% White = 92% Cancer diagnosis = all types of cancer Treatment = inpatient, outpatient, or RT	• Mediation analyses indicated that pain influences fatigue directly as well as indirectly by its effect on sleep • About 20% of the variation in fatigue is explained by pain
Abbreviations: CTX, chemotherapy; RT, radiation therapy.		

Table 2.
Studies That Empirically Derived Symptom Clusters in Oncology Patients

Study, Purpose, Instrument Used to Measure Symptoms, and Method Used to Derive the Symptom Cluster(s)	Sample Characteristics	Specific Symptom Cluster(s) Identified and Other Findings
Cleeland et al, 2000¹⁸ <u>Purpose:</u> To develop the MDASI, a brief measure of the severity and impact of cancer-related symptoms <u>Instrument:</u> MDASI <u>Method:</u> Hierarchical cluster analysis and factor analysis	N = 527 patients Age = 55 years Female = 55% Cancer diagnosis = all types of cancer Treatment = all types of treatment	<u>Specific Symptom Cluster(s) Identified</u> Two factors were found: (1) a general symptom severity factor (ie, pain, fatigue, disturbed sleep, distress, shortness of breath, drowsiness, dry mouth, sadness, memory problems, numbness); (2) a gastrointestinal factor (ie, nausea, vomiting) <u>Other Findings</u> While cluster analysis was used to create symptom clusters based on patients' responses to the MDASI and a dendrogram is provided in the paper, the data for specific symptom clusters were not reported
Gift et al, 2003⁷ <u>Purpose:</u> To determine whether the symptom cluster identified at the time of diagnosis remained 3 and 6 months later and whether there was a difference in the mean number of symptoms and the mean severity of symptoms over time <u>Instrument:</u> Physical Symptom Experience Tool <u>Method:</u> Cronbach alpha rather than confirmatory factor analysis	N = 112 patients Age = 72 years Female = 48% Cancer diagnosis = lung Treatment = surgery, CTX, or RT	<u>Specific Symptom Cluster(s) Identified</u> A single symptom cluster with seven symptoms was identified (ie, fatigue, weakness, nausea, vomiting, loss of appetite, weight loss, and altered taste sensations) <u>Other Findings</u> - The cluster of seven symptoms had internal consistency that remained at 3 and 6 months - The mean symptom severity and the number of symptoms at diagnosis were correlated with later ratings, but decreased in severity over time
Gift et al, 2004⁶ <u>Purpose:</u> To identify the number, type, and combination (cluster) of symptoms experienced by patients with lung cancer <u>Instrument:</u> Physical Symptom Experience Tool <u>Method:</u> Exploratory maximum likelihood factor analysis	N = 220 patients Age = 72 years Female = 41% Married/partnered = 61% White = 91% Cancer diagnosis = lung cancer Treatment = Surgery, CTX, RT	<u>Specific Symptom Cluster(s) Identified</u> A single symptom cluster with seven symptoms was identified (ie, fatigue, weakness, nausea, vomiting, loss of appetite, weight loss, and altered taste sensations) <u>Other Findings</u> - Initial staging of cancer, the number of comorbid conditions, and being treated with CTX emerged as significant predictors of the symptoms reported - Correlations were found among the number of symptoms reported, symptom severity, and limitations attributed to the symptoms
Bender et al, 2005¹⁰ <u>Purpose:</u> To compare the prevalence of symptoms attributable to breast cancer or its treatment and to identify and describe symptom clusters across three phases of disease (ie, early stage, adjuvant CTX, metastatic disease) using data from three different studies <u>Instrument:</u> Thirteen breast symptoms common across the three studies were derived from multiple instruments <u>Method:</u> Hierarchical cluster analysis	N = 154 patients Age = 50.2 years Female = 100% Cancer diagnosis = breast cancer Treatment = surgery, CTX, RT	<u>Specific Symptom Cluster(s) Identified</u> A single symptom cluster composed of at least six symptoms was identified in each sample of women with breast cancer. The six symptoms that were common across all three groups of patients were fatigue, feeling a lack of energy, decreased physical strength/weakness, feeling depressed or blue, feeling anxious or nervous, and loss of concentration <u>Other Findings</u> - Problems with memory also clustered but only in the non- metastatic breast cancer samples - Difficulty sleeping, aching muscles and joints, and backaches were symptoms that were part of the symptom cluster in women with early stage breast cancer

Table 2.
Continued

Study, Purpose, Instrument Used to Measure Symptoms, and Method Used to Derive the Symptom Cluster(s)	Sample Characteristics	Specific Symptom Cluster(s) Identified and Other Findings
Francoeur, 2005⁹ <u>Purpose:</u> To predict variation in depressive affect that could be attributed to symptom clusters <u>Instrument:</u> List of physical symptoms rated using a Likert scale on the degree of difficulty in controlling each physical symptom over the past month <u>Method:</u> Curvilinear and moderator regression analyses	N = 268 patients Age = 62.7 years White = 90.7% Cancer diagnosis = all types of cancer Treatment = surgery, RT	<u>Specific Symptom Cluster(s) Identified</u> The effects of a variety of symptom clusters on depression were evaluated as part of this study <u>Other Findings</u> • After accounting for sleep problems associated with fever, when fever control is low and pain increases, depression increases dramatically • Depressive affect is heightened when nausea/vomiting is accompanied by a high level of fever • Depression is heightened when pain is accompanied by a high level of weakness
Chen and Tseng, 2006¹² <u>Purpose:</u> To understand which cancer-related symptoms cluster together and to test the conceptual meanings of the revealed clusters <u>Instrument:</u> MDASI <u>Method:</u> Exploratory factor analysis with principal-axis factoring with oblique rotation	N = 151 patients Age = 50.8 years Female = 40.4% Cancer diagnosis = all types of cancer Treatment = CTX or other	<u>Specific Symptom Cluster(s) Identified</u> Three symptom clusters were identified: (1) Sickness symptom cluster (ie, pain, fatigue, sleep disturbance, lack of appetite, drowsiness); (2) Gastrointestinal symptoms cluster (ie, nausea, vomiting); (3) Emotional symptom cluster (ie, distress, sadness) <u>Other Findings</u> • Patients with pain and with advanced disease had significantly higher mean scores in the sickness symptom cluster than patients without pain and earlier stage disease • Patients' functional status was negatively correlated with mean scores in the sickness symptom cluster • Patients receiving CTX demonstrated significantly higher scores in the gastrointestinal symptom cluster than patients undergoing other treatments • Patients with anxiety and depression had significantly higher mean scores in the emotional symptom cluster than those patients without anxiety or depression
Walsh and Rybicki, 2006¹¹ <u>Purpose:</u> To identify the presence and composition of any symptom clusters in patients referred for palliative care <u>Instrument:</u> List of 38 symptoms that were empirically derived from the traditional system review routinely used in medical history taking <u>Method:</u> Agglomerative hierarchical cluster analysis	N = 922 patients Age = 65 years Female = 44% Cancer diagnosis = all types of cancer Treatment = palliative care	<u>Specific Symptom Cluster(s) Identified</u> Seven symptom clusters were identified: (1) Fatigue-anorexia-cachexia cluster (easy fatigue, weakness, anorexia, lack of energy, dry mouth, early satiety, weight loss, taste changes); (2) Neuropsychological cluster (sleep problems, depression, anxiety); (3) Upper gastrointestinal cluster (dizzy spells, dyspepsia, belching, bloating); (4) Nausea and vomiting cluster (nausea, vomiting); (5) Aerodigestive cluster (dysphagia, dyspnea, cough, hoarseness); (6) Debility cluster (edema, confusion); and (7) Pain cluster (pain, constipation) <u>Other Findings</u> • Highly prevalent symptoms did not cluster with each other

Abbreviations: MDASI, M.D. Anderson Symptom Inventory; CTX, chemotherapy; RT, radiation therapy

within a cluster is the concept of “sickness behavior” that was first described in animals.²¹

CYTOKINE-INDUCED SICKNESS BEHAVIOR

In a recent review, Cleeland et al²² suggest that the symptoms of cancer and cancer treatment may be due, in part, to a shared biologic mechanism, cytokine-induced sickness behavior. Sickness behavior can be observed in sick animals^{23,24} or induced with the administration of the pathophysiological components of bacteria (eg, lipopolysaccharide). Predictable physiological responses occur in animals to lipopolysaccharide include fever, pain, wasting, and increased activity in the hypothalamic-pituitary-adrenal axis and the autonomic nervous system.²⁵ These animals also exhibit behaviors such as a general decrease in activity, somnolence, cognitive impairment, decreased social interaction and exploration, decreased sexual activity, and decreased food intake. These physiological and behavioral responses in animals are remarkably similar to symptoms within the symptom clusters identified in cancer patients.^{11,12,18}

Most of the research in animals suggests that sickness behavior requires communication between the brain and the immune system to orchestrate the array of physiological and behavioral responses. This communication activates a cascade of pro-inflammatory cytokines (eg, interleukin-1 [IL-1], IL-6, tumor necrosis factor- α) that activate immune cells. Studies in animals demonstrate that the injection of inflammatory cytokines results in the characteristic sickness behavior described above and that the injection of cytokine antagonists attenuates this behavior.^{22,26-32}

Some clinical evidence exists to support the hypothesis that some of the most common symptoms that co-occur in patients with cancer (eg, pain, fatigue, sleep disturbance, depression) may occur through the release of pro-inflammatory cytokines. For example, patients with hepatitis C who receive treatment with interferon- α experience the symptoms of pain, fatigue, cognitive impairment, and depression.³³ A similar “sickness syndrome” was observed in patients with renal cell cancer who received IL-2²² as well as in patients who receive interferon α .^{34,35} In addition, elevated levels of endogenous IL1- β and IL-6 were found in symptomatic individuals with

viral infections.³⁶ Thus, perturbations in the molecular détente between pro- and anti-inflammatory cytokines can result in sickness behavior, leading us to suggest that depletion of anti-inflammatory cytokines could also contribute to sickness behavior.

While cytokine-induced sickness behavior represents an intriguing mechanistic hypothesis to explain the co-occurrence of multiple symptoms or symptom clusters in patients with cancer, based on the findings from the research studies presented in Tables 1 and 2, this mechanism cannot account for all of the clusters reported to date. If this mechanism were the only mechanism that was activated during cancer or cancer treatment, one might expect to find the same symptom clusters across studies. An examination of Table 2 clearly shows the lack of consistency in the number of symptom clusters as well as in the specific symptoms within various clusters in the samples studied to date. Differences in study designs; in the analytic methods used to create the symptom clusters; and in the demographic (eg, age, gender, ethnicity) and clinical characteristics of the sample could contribute to the variance in the number and types of symptom clusters.

IMPLICATIONS FOR PRACTICE AND RESEARCH

The science of symptom cluster research is still in its infancy. This line of inquiry is extremely important to reduce the symptom burden that patients experience on a daily basis. However, based on the symptom cluster studies conducted to date, it is not possible to draw definitive conclusions about whether or not there is a biologic basis for the symptom clustering.

The need exists to determine which symptoms co-occur within the context of a specific cancer diagnosis and cancer treatment versus which symptoms co-occur in a consistent pattern regardless of diagnosis or treatment. Both cross-sectional and longitudinal studies of symptom clusters are needed to determine which symptoms constitute a “true symptom cluster.” Based on the findings published to date, one cannot draw any definitive conclusions about the number or the types of symptoms that constitute a symptom cluster. That said, the cytokine-induced model of sickness behavior constitutes a plausible hypothesis to investigate a common biologic mechanism

for cancer-related symptom clusters. In addition, both animal and human studies need to be conducted on the gastrointestinal cluster of nausea

and vomiting. In addition, researchers must search for biologic mechanisms that could underlie specific symptom clusters.

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