

# The Elusive Concept of the Symptom Cluster

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**Purpose/Objectives:** To provide an integration and synthesis of literature on the definition and importance of the symptom cluster, theoretical frameworks to explain it, analysis strategies to identify it, interventions to alleviate it, and suggestions for future research.

**Data Sources:** A literature review from 1995–2007 was conducted using MEDLINE®. Clinical guidelines, descriptive research, intervention studies of multiple symptoms, and theoretical and conceptual articles were examined. Articles were reviewed if at least two of the four symptoms of interest were examined in relation to one or more other symptoms. Conceptual models were included if they explained or allowed for the notion of a symptom cluster.

**Data Synthesis:** Four symptoms were examined as a candidate symptom cluster for this analysis: fatigue, insomnia, pain, and depression. Symptom clusters were identified by expert opinion, group comparisons, shared variance among symptoms (including factor analysis and mediation analysis), identification of subgroups, influence of symptoms on patient outcomes, or the identification of a common underlying mechanism. Regardless of the method chosen for identifying a symptom cluster, the substantial evidence showed that various combinations of the target symptoms formed a symptom cluster.

**Conclusions:** Although the findings suggest that fatigue, insomnia, pain, and depression constitute a viable cluster for further study, more research is needed to define the cluster and describe its underlying mechanisms. Addressing multiple symptoms is beneficial in reducing negative patient outcomes; however, more work needs to be done to understand the efficacy of intervention for symptom clusters.

**Implications for Nursing:** When conducting symptom assessment, healthcare providers should address the four symptoms (fatigue, insomnia, pain, and depression) targeted in this review because evidence of clustering exists. Guidelines provided by the National Comprehensive Cancer Network for fatigue and distress provide algorithms and decision trees for assessment and management.

## Key Points . . .

- Because patients with cancer often have multiple symptoms, the possibility that symptoms cluster together in a systematic way cannot be ignored.
- Fatigue, insomnia, pain, and depression are the most prevalent and distressing symptoms for patients with cancer.
- The evidence suggests that fatigue, insomnia, pain, and depression constitute a symptom cluster and that addressing these symptoms is beneficial in reducing negative patient outcomes.

that can be used to guide understanding of this construct, strategies that have been used to identify a symptom cluster, interventions used to alleviate a symptom cluster, and suggestions for future research.

Four symptoms were examined as a candidate symptom cluster for this analysis: fatigue, insomnia, pain, and depression. These four symptoms were selected because fatigue and insomnia are among the most prevalent symptoms reported by patients with cancer (Berger et al., 2005; Cella, Davis, Breitbart, & Curt, 2001; Curt et al., 2000; Homsy et al., 2006; Vogelzang et al., 1997) and pain and depression are among the most distressing symptoms (Cleeland et al., 1994; Foley, 2004; Homsy et al., 2006). A literature review from 1995–2007 was conducted. Clinical guidelines, descriptive (nonintervention) studies, intervention studies of multiple symptoms, and theoretical and conceptual articles were examined. Articles were selected for review if they examined at least two of the four symptoms in relation to one or more other symptoms. Conceptual models were included if they explained or allowed for the notion of a symptom cluster. Examples from published studies were used to illustrate different approaches to the identification of and interventions for a symptom cluster. Although the literature review was not exhaustive, it was comprehensive enough to allow for a thorough analysis and synthesis of current scientific thought.

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Most people involved in cancer symptom research or clinical practice have at least a passing interest in symptom clusters because patients with cancer often have multiple symptoms. Given this reality, the possibility that symptoms could cluster together in a systematic way cannot be ignored. Dodd, Janson, et al. (2001) first called for consideration of the concept of the symptom cluster as a basis for a rational approach to symptom management. Figuring out how and why symptoms are related and how they influence patient outcomes is important. Cancer symptom management would benefit if an integrated intervention plan existed for a cluster of symptoms based on a clear understanding of which symptoms are likely to cluster, when clustering is likely to occur, and how a symptom cluster affects patient outcomes.

Since Dodd, Miaskowski, and Paul (2001) first issued the challenge to study symptom clusters, a significant amount of research has focused on the phenomenon. This article will integrate and synthesize literature examining the definition and importance of the symptom cluster, theoretical frameworks

## The Concept of a Symptom Cluster

Kim, McGuire, Tulman, and Barsevick (2005) defined a symptom cluster as a stable group of two or more concurrent symptoms that are related to one another and independent of other symptoms or symptom clusters. Whether two or three symptoms constitute a cluster is debatable, but the two-symptom definition was chosen for this synthesis because it allows for a broader exploration of the literature (Dodd, Miaskowski, et al., 2001; Dodd, Miaskowski, & Lee, 2004; Miaskowski, Dodd, & Lee, 2004). Dodd, Miaskowski, et al. (2001) and Miaskowski et al. (2004) suggested that symptoms in a cluster could share covariance, a common etiology, or a common influence on patient outcomes. Historically, symptom clusters were used to diagnose most diseases prior to the 20th century (Aronowitz, 2001). Today, symptom clusters are used in diagnosis when a biologic mechanism is not well understood, such as premenstrual syndrome (Woods, Mitchell, & Lentz, 1999) and some psychiatric disorders (American Psychiatric Association, 2000).

The scientific basis for the symptom cluster in oncology is early in its development. Using the analogy of a star cluster could be instructive regarding some of the issues related to this concept. Star clusters have fascinated people for thousands of years. The Pleiades, perhaps the most famous star cluster, was named by the ancient Greeks for nine of the brightest stars in the formation. The same group of stars was named “the six pigs in heaven” by Cherokee Native Americans. Modern telescopes have shown that this cluster actually contains thousands of stars. With regard to the symptom cluster, the proper tools and methods for studying it have not been determined. Like the ancient stargazers, little is known about how many symptoms and which specific symptoms should be included in the cluster of interest. Instead of the four symptoms selected for this review, the cluster could be expanded to include other symptoms as well.

Recognizing and understanding the scientific basis for symptom clusters could help clinicians and scientists in several ways. A cluster could provide the basis for identifying or diagnosing a syndrome or condition related to cancer or its treatment and help identify subgroups of individuals with different or unique symptom profiles. A symptom cluster also could guide the search for a common etiology or mechanism underlying a group of symptoms and could provide a basis for understanding how multiple symptoms are related to one another.

## Theoretical Frameworks

### The Symptom Management Model

Although the Symptom Management Model does not address the symptom cluster specifically, it is designed to accommodate the concept. The Symptom Management Model depicts the interrelationship among three components: the symptom experience, symptom management strategies, and patient outcomes (Dodd, Janson, et al., 2001). The symptom experience is a patient's perception of the frequency, intensity, distress, and meaning of a single or multiple symptoms as they are expressed. Symptom management is a dynamic process in which strategies evolve and change over time. The primary outcome of symptom management is symptom status. Other outcomes are functional status, emotional state, self-care, quality of life (QOL), cost, mortality, and morbidity. Each component of the model can be influenced by every other component.

## The Theory of Unpleasant Symptoms

The Theory of Unpleasant Symptoms presents a more linear view of symptoms beginning with antecedents that shape the symptom experience (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). Physiologic antecedents include pathologic problems and energy factors such as nutrition. Psychological factors include mental state and reactions to illness. Situational factors include lifestyle and social support. Symptoms can occur as separate entities or concurrently as a symptom cluster. Characteristics of symptoms include intensity, distress, quality, and duration. Consequences are the outcomes or effects of the symptom experience, which include functional status, cognitive functioning, and physical activity level. Each component of the model has a feedback loop to the other components. Lenz et al. asserted that concurrent symptoms are likely to result in an experience that is multiplicative rather than additive. They suggested that symptoms could interact to influence outcomes or symptoms could be mediators between antecedents and consequences; these propositions have not been tested.

### The Symptoms Experience Model

The Symptoms Experience Model, which builds on the Theory of Unpleasant Symptoms and the Symptom Management Model, expands an understanding of the meaning of the symptoms experience. Two forms of meaning are proposed (Armstrong, 2003). Situational meaning is the perception of the impact of a symptom(s) on a patient's daily life and the capacity to handle it. For example, fatigue could limit a patient's ability to socialize with friends. Existential meaning is the global representation of a patient's place in the world, such as a sense of mortality or vulnerability; conversely, the meaning could be positive, such as increased family closeness. Understanding of the subjective meaning of a symptom cluster has yet to be developed, possibly using qualitative methodologies.

### The Symptom Interaction Framework

As in the Theory of Unpleasant Symptoms, Parker, Kimble, Dunbar, and Clark (2005) described the possibility of “synergistic relationships or interactions among symptoms” (p. 209) in the Symptom Interaction Framework; however, a definition of the term interaction was not provided, so whether the definition was intended to describe statistical interaction or a more colloquial sense of multiple symptoms having a more pronounced effect on each other or outcomes is uncertain.

Parker et al. (2005) also argued that the presence of multiple symptoms could be the result of multiple underlying causal mechanisms. A symptom is defined as the subjective perception of an alteration in a bodily process or function. Mechanism is used to describe any alteration of a process or function that could explain the presence of a symptom or symptoms. Several domains of mechanisms have been identified, including biologic, psychological, behavioral, and sociocultural. When multiple symptoms are present, a combination of mechanisms could be required to explain the symptom experience.

For example, a biologic explanation for the presence of insomnia and pain is that the raphe system and reticular formation in the medulla and pons of the brain are critical centers for sleep regulation and pain modulation (Parker et al., 2005). In the sociocultural domain, cultural background could influence perception of insomnia and pain. From the perspective of the psychological domain, depression could

cause sleep disturbances and altered pain response. In the behavioral domain, the use of pain medication could result in sleep disturbances. One or more of these mechanisms could explain the presence of pain and insomnia. Because symptoms involve the perception and interpretation of biologic changes, exploring causal mechanisms from all of these perspectives would be appropriate.

The four models have several features in common (see Table 1). Each model can incorporate the idea of multiple symptoms or a symptom cluster. The models also present ideas about factors that influence a symptom cluster and about the effect of a symptom cluster on patient outcomes. However, none of the models provides specific criteria by which a symptom cluster can be identified and differentiated from other clusters or random symptoms. Currently, what defines a symptom cluster is in the eye of the beholder.

## Identifying a Symptom Cluster

The obvious question is, “How have scientists tried to identify a symptom cluster?” A number of strategies have been used, including expert opinion, group comparisons, identification of shared variance among symptoms such as latent factors and mediators, identification of patient subgroups, identification of a common underlying mechanism, and influence on patient outcomes.

### Expert Opinion

The National Comprehensive Cancer Network ([NCCN], 2006a, 2006b, 2006c) developed guidelines for the assessment and management of cancer-related fatigue, pain, and distress. The guidelines are among the best available guidance for management of cancer-related symptoms. Each set of symptom guidelines was developed by a multidisciplinary panel of experts with clinical or scientific expertise about a particular

symptom. In the NCCN guidelines on fatigue (2006b), assessment of pain, emotional distress, and sleep disturbance as potential causes of fatigue is recommended. The NCCN guidelines on distress (2006c) called for the assessment of fatigue, pain, and sleep disturbance as potential causative factors related to distress. Recognizing that the presence of one symptom points to the need for assessment of other related symptoms provides expert opinion that the symptoms form a cluster. This method of identifying a symptom cluster is the most relevant clinically because it is based on clinical observation and directed toward clinical symptom management.

### Group Comparisons

One way to establish whether symptoms are related is to determine if an increment in one symptom is associated with an increment or decrement in another symptom or group of symptoms (Beck, Dudley, & Barsevick, 2005; Given, Given, Azzouz, Kozachik, & Stommel, 2001; Hopwood & Stephens, 2000). For example, Beck et al. found that every increment in pain severity was associated with an increase in fatigue and, separately, an increase in sleep disturbance. Given et al. (2001) examined the effect of pain and fatigue on the number of other symptoms reported by older adult patients with cancer. Individuals who did not report pain or fatigue had the lowest total symptom level. Total symptoms increased with each symptom and were highest for patients with pain or fatigue. The result suggests that pain and fatigue could be sentinel symptoms that play a significant role in the symptom experience. If the presence of pain and fatigue is associated with greater symptom burden, the alleviation of pain and fatigue could have far-reaching effects on other symptoms.

### Evidence of Shared Variance

Evidence of a symptom cluster may be based on shared variance (Dodd et al., 2004; Miaskowski, 2006). Various studies

**Table 1. Models of Symptoms and Symptom Clusters**

Model	Definition	Components of Model	Mechanisms	Outcomes	Unique Features
Symptom Management Model	Subjective experience reflecting changes in biopsychosocial functioning, sensations, or cognition	Symptoms Symptom management Outcomes	Not addressed	Symptom status Emotional state Self-care Quality of life Cost Mortality Morbidity	Addresses the concept of symptom management Posits interrelationships among the model components
Theory of Unpleasant Symptoms	Perception of change in normal functioning as experienced by an individual	Antecedents Symptoms Consequences	Not addressed	Functional status Cognitive functions Physical performance	Proposes that <ul style="list-style-type: none"> <li>Symptoms could interact to influence outcomes.</li> <li>Symptoms could be mediators between antecedents and outcomes.</li> </ul>
Symptoms Experience Model	Perception of the frequency, intensity, distress, and meaning that occurs as symptoms are produced and expressed	Antecedents Symptoms Consequences	Not addressed	Adjustment to illness Quality of life Mood Functional status Disease progression Survival	Proposes that the meaning of symptoms (situational or existential) is an important attribute
Symptom Interaction Framework	Subjective perception of alteration in normal bodily function and sensation	Not addressed	Psychological Physiologic Behavioral Sociocultural	Not addressed	Addresses the potential mechanism(s) of single or multiple symptoms



have examined shared variance between and among groups of symptoms using bivariate correlations. Usually the studies had one symptom as a central focus. For example, Bower et al. (2000) studied fatigue in almost 2,000 breast cancer survivors and found it was associated with pain, depression, and insomnia. Glover, Dibble, Dodd, and Miaskowski (1995) studied pain in 200 patients with cancer with a variety of diagnoses and treatments and demonstrated that pain was associated with depression, fatigue, and anxiety. Many correlation analyses have shown that specific symptoms were moderately correlated with other symptoms (Berger & Farr, 1999; Berger & Higginbotham, 2000; Bower et al.; Broeckel, Jacobsen, Horton, Balducci, & Lyman, 1998; Carpenter et al., 2004; Fillion, Gelin, Simard, Savard, & Gagnon, 2003; Glover et al.; Hann et al., 1997; Jacobsen et al., 1999; Miaskowski & Lee, 1999; Smets et al., 1998; Stone et al., 1999; Stone, Hardy, Huddart, A'Hern, & Richards, 2000; Stone, Richards, A'Hern, & Hardy, 2000, 2001). On the basis of shared variance, a group of symptoms including fatigue, insomnia, pain, and depression could constitute a cluster.

**Identification of latent factors:** Another strategy used to examine shared variance among groups of symptoms is factor analysis. Factor analysis is used to discover coherent subsets of variables that are correlated with one another but independent of other subsets. The factors are believed to reflect underlying processes responsible for correlations among variables (Tabachnick & Fidell, 2001). The validity of each factor is tested by examining relationships with other variables. The potential for identifying an underlying process or mechanism makes factor analysis attractive in symptom cluster research. If a cluster of symptoms is identified via factor analysis, hypotheses could be tested about the mechanism or process that accounts for the clustering.

Chen and Tseng (2006) evaluated 13 symptoms in 151 Taiwanese outpatients with a variety of cancers. Factor analysis of symptom scores revealed three factors. Factor 1 included the symptoms of pain, fatigue, sleep disturbance, lack of appetite, and drowsiness; it was labeled "sickness behavior symptom cluster" referring to a symptom cluster observed by Lee et al. (2004) in animals that is linked to a proposed underlying biologic mechanism. Factor 2 was described as a gastrointestinal symptom cluster including nausea and vomiting, and factor 3 was defined as an emotional symptom cluster that included distress and sadness. Hypotheses could be tested about the mechanism underlying each symptom cluster to determine the nature of the relationship among the symptoms. For example, hypotheses have been proposed about cytokines being responsible for the "sickness behavior symptom cluster" (Lee et al.).

Gift, Jablonski, Stommel, and Given (2004) analyzed data from 220 newly diagnosed older adult patients with lung cancer who completed a 32-item symptom questionnaire. Data for the factor analysis were obtained four to eight weeks after diagnosis. Although four factors were identified, only the first factor produced item loadings higher than 0.4 for each of the seven symptoms. This group of symptoms (fatigue, weakness, appetite loss, weight loss, altered taste, nausea, and vomiting) was identified as the "lung cancer symptom cluster."

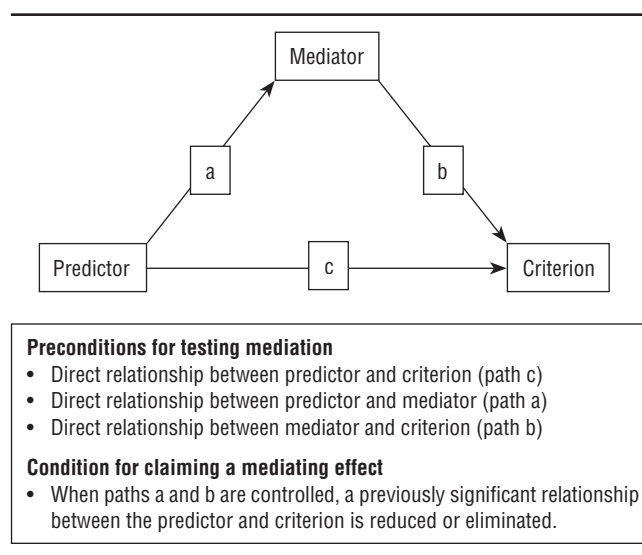
Differences in the results of each of the factor analytic studies could be caused, in part, by the patient population studied, the symptoms measured, the timing of measures, or characteristics of the factor analysis procedure. Chen and Tseng

(2006) studied a mixed population with varied diseases and therapies using a 13-item symptom scale. Gift et al. (2004) reduced variability from the type of cancer by studying a single cancer diagnosis using a 32-item symptom scale. An issue highlighted by differences in the results of the studies is that a symptom cluster is defined, in part, by which symptoms are measured. Results of the two studies might have been more alike if the same symptoms had been measured.

Another reason for variation in factor analysis results could be differences in factor rotation by investigators. Once the factors have been extracted, the number of possible rotations to increase interpretability is infinite. All of the solutions account for the same amount of explained variance, but the factors may be defined somewhat differently (Tabachnick & Fidell, 2001). The final choice is based on the researcher's evaluation of the most usable and interpretable solution.

**Identification of mediators:** Researchers have identified symptom clusters by examining the way symptoms influence one another using an analytic strategy called mediation analysis (Baron & Kenny, 1986). A variable is a mediator when it accounts for the relationship between a predictor and a criterion. Mediators can speak to how or why certain symptoms are related. Several conditions are necessary to establish mediation. In Figure 1, the first three statements describe the prerequisites that must be present to test for mediation; a bivariate relationship must be present between each pair of variables. The fourth statement is the test of mediation. With the mediator in the equation, a previously significant relationship between the predictor and criterion is reduced or eliminated.

A few examples exist of symptom mediation in patients with cancer (Barsevick, Dudley, & Beck, 2006; Beck et al., 2005; Williamson & Schulz, 1995). Beck et al. examined the interrelationships among symptoms of pain, fatigue, and sleep disturbance. Pain and sleep disturbance predicted fatigue. The two



**Figure 1. The Mediation Pathway**

*Note.* From "The Moderator-Mediator Variable Distinction in Social Psychological Research: Conceptual, Strategic, and Statistical Considerations," by R.M. Baron and D.A. Kenny, 1986, *Journal of Personality and Social Psychology*, 51, p. 1176. Copyright 1986 by the American Psychological Association. Adapted with permission.

symptoms also were associated with each other. The mediation analysis demonstrated that when the relationship between pain and sleep disturbance was controlled, a previously significant association between pain and fatigue was reduced while sleep disturbance maintained a strong association with fatigue. The analysis provides a more complete explanation of the way in which the group of symptoms is related. Pain is related directly to fatigue and influences it indirectly because it disrupts sleep. The result has implications for symptom management. Efforts to reduce fatigue need to consider pain reduction and sleep enhancement.

In another example of mediation, the symptoms of fatigue and depression were examined with functional status as a mediator (Barsevick et al., 2006). The findings demonstrated that functional status was a mediator between the symptoms. Using bivariate correlation, the research associated higher fatigue with poor functional status and depressive symptoms; however, after the study controlled for fatigue and functional status, the relationship between fatigue and depressive symptoms was diminished, which suggests that considering functional status in fatigue management is important because of its association with depressive symptoms. An intervention such as energy conservation could be beneficial because it addresses the problem of decreased functional status during cancer therapy.

### Identification of Subgroups

An interesting way to identify a symptom cluster is by using cluster analysis to classify variables into groups with high internal (within a cluster) homogeneity and high external (between clusters) heterogeneity (Hair & Black, 2000). Symptoms or people can be sorted into similar groups that are different from other groups. Then, a search for an underlying mechanism or process (biologic, psychological, behavioral, or sociocultural) to explain the differences can be undertaken (Parker et al., 2005). Cluster groups also could help to sort people according to need for clinical intervention.

Several studies have been reported in which symptoms were cluster analyzed (Bender, Ergyn, Rosenzweig, Cohen, & Sereika, 2005; Walsh & Rybicki, 2006). For example, Walsh and Rybicki conducted a cluster analysis of 25 symptoms reported by 922 patients with advanced cancer to determine whether clusters of symptoms could be identified. Clusters were selected using the criterion that symptom correlations in the cluster were greater than or equal to 0.68. Seven clusters were identified that were relevant to individuals receiving end-of-life care: fatigue-anorexia-cachexia, neuropsychological, upper gastrointestinal, nausea-vomiting, aerodigestive, debility, and pain. The investigators noted that symptom groups could be associated with different pathophysiology. They also suggested that different groupings were likely to be important therapeutically because treatment of one symptom could influence or be influenced by another symptom.

Other researchers have used cluster analysis to identify patient groups with similar symptom profiles (Miaskowski et al., 2006; Nagel, Schmidt, Strauss, & Katenkamp, 2001; Trask & Griffith, 2004). Miaskowski et al. (2006) cluster analyzed a heterogeneous group of 191 adults with cancer with regard to four symptoms: fatigue, insomnia, pain, and depression. The final solution identified four cluster patterns: (a) all symptoms high (N = 68, 35%), (b) all symptoms low (N = 67, 35%), (c) high fatigue, low pain (N = 28, 15%), and

(d) low fatigue, high pain (N = 28, 15%). The analysis could be a first step in sorting out groups whose symptoms share a common mechanism such as differences in gene expression or psychological traits. The analysis also could be clinically relevant in the identification of groups needing more or less symptom intervention.

### Common Underlying Mechanisms

The term “underlying mechanism” in the context of symptom management conjures the idea of physiologic mechanisms. In fact, interest is growing in a common biologic mechanism underlying a group of symptoms (Cleeland et al., 2003). Sickness behavior has been described by a symptom profile that can include anorexia, cachexia, fever, nausea, fatigue, anhedonia (loss of pleasure), pain, and impaired learning (Lee et al., 2004). Sickness behavior has been induced in animals by administration of exogenous cytokines, infectious agents, or endotoxins. The same inflammatory cytokine-induced process that gives rise to sickness behavior in animals could be responsible for a similar group of symptoms typically associated with cancer and its treatment in humans.

Despite interest in finding a biologic mechanism in humans to explain many of the symptoms associated with cancer and its treatment, only a few studies have been reported. In the factor analysis by Chen and Tseng (2006) described earlier, the first factor (pain, fatigue, sleep disturbance, anorexia, and drowsiness) included several of the symptoms characterized as sickness behavior. Another study examined the symptoms of sickness behavior in patients being treated with radiotherapy for bone metastases and pain (Francoeur, 2005). Analyses were based on the assumption that depression was the psychological manifestation of the malaise of sickness behavior. The hypothesis was that pain and other symptoms would interact to predict depression. The hypothesis was supported; interactions between pain and fatigue, pain and weight loss, pain and fever, and sleep and fever predicted depressive symptoms. The study provided the first evidence that symptom pairs can have a synergistic or interaction effect in predicting patient outcomes as suggested by two of the theories reviewed (Dodd, Janson, et al., 2001; Lenz et al., 1997). In addition, the study was the first test of the sickness behavior hypothesis.

### The Effect of a Symptom Cluster on Outcome

Having explored how symptoms in a cluster are related to each other, consideration must be given to the effect of a symptom cluster on outcomes or consequences. The first oncology study to focus on a symptom cluster was by Dodd, Miaskowski, et al. (2001). They proposed that a symptom cluster (including pain, fatigue, and sleep insufficiency) would be associated with functional status; their hypothesis was correct. The presence of each symptom incrementally explained more variance in functional status. No significant interactions existed among any of the symptom variables, so their effects were additive rather than multiplicative.

Gift et al. (2004) and Gift, Stommel, Jablonski, and Given (2003) also looked at the effect of the lung cancer symptom cluster on two consequences: physical function and role limitations. The number of symptoms reported and the severity of those symptoms were related to the two indicators of functional status. Redeker, Lev, and Ruggiero (2000) examined the effect of a group of symptoms—fatigue, insomnia, anxiety, and depression—on QOL in a mixed sample of 263 patients receiving

**Table 2. Studies of Systematic Symptom Assessment**

Study	Sample	Intervention	Results
Homsí et al., 2006	200 patients receiving palliative care	Open-ended assessment followed by systematic assessment	Open-ended assessment yielded a median of one symptom reported; systematic assessment yielded a median of 10 symptoms.
McLachlan et al., 2001	450 mixed diagnoses, a third in active treatment	Computerized completion of QOL scale; results given to MD in clinic with follow-up by RN (one contact) versus usual care	No difference in QOL, psychosocial function, or satisfaction with care
Sarna, 1998	48 patients with newly diagnosed lung cancer	Structured RN assessment (six contacts) versus usual care	Lower symptom distress in assessment group
Taenzer et al., 2000	53 patients with lung cancer	Computerized completion of a QOL scale; results given to MD (one contact) versus QOL scale completed but not given to MD	Increased discussion of QOL issues; increased charting of QOL issues; trend toward more MD actions in response to QOL in assessment group
Velikova et al., 2004	286 patients beginning cancer treatment	Computerized completion of QOL scale; results to MD (every contact for six months) versus QOL scale completed but not given to MD versus usual care	Increased overall well-being in QOL and symptoms in 64% of encounters

MD—doctor of medicine; QOL—quality of life

chemotherapy. The four symptoms together explained 47% of the variance in QOL. The symptoms that contributed most to the explanation of variance were depression, fatigue, and anxiety (Redeker et al.).

Given et al. (2001) examined the incremental effect of a symptom cluster (including fatigue, insomnia, and pain) on functional status in 826 older adult patients with cancer. In the breast cancer cohort, when individuals with none of the cluster symptoms were compared with individuals who reported one, two, or all three of the symptoms, the latter groups were at incrementally greater risk of being in a lower functioning group six to eight weeks after diagnosis. For the colon and lung cancer cohorts, having two or three symptoms predicted low functional status; for the prostate cancer group, having all three symptoms predicted low functional status. If the findings that more symptoms predict worse functioning are correct, an intervention to prevent or alleviate symptoms may result in maintained or improved functional status.

Regardless of the method chosen for identifying a symptom cluster, combinations of the same symptoms (fatigue, insomnia, pain, and depression) have been associated with each other or a latent factor or have characterized a subgroup of individuals; these symptoms together have predicted or been incrementally related to a common outcome; and a common biologic mechanism may be present. Taken together, the results suggest that fatigue, insomnia, pain, and depression, the four most common and distressing symptoms, could represent a symptom cluster.

Although the findings suggest that fatigue, insomnia, pain, and depression is a viable cluster for further study, more research with better descriptions of the symptom cluster and an exploration of all of the potential underlying mechanisms (physiologic, psychological, behavioral, and sociocultural) is needed (Lee et al., 2004; Parker et al., 2005). Clear, defining characteristics of a symptom cluster should be established so that additional symptoms can be ruled in or out. Understanding the clinical meaning of the inclusion or exclusion of additional symptoms and the relationship of symptom clusters to disease and treatment is important. More information is

needed about how a symptom cluster influences outcomes. Finally, consensus is needed regarding the measurement of symptom clusters.

Despite the promise of symptom cluster research, the concept is from a long way from being clinically useful. The identification of a symptom cluster does not mean that individuals in a clinical situation will report all symptoms in the cluster at a similar level of severity. After identifying a lung cancer symptom cluster, Gift et al. (2004) noted that 11% of their sample reported none of the cluster symptoms and only 5% reported all seven symptoms. As the number of cluster symptoms increased, the number of individuals reporting those symptoms was smaller and smaller. Likewise, Miaskowski et al. (2006) identified four different cluster patterns of fatigue, insomnia, pain, and depression. However, more than a third of the sample was in a group with all low symptoms.

Clinically, every symptom in a cluster is not likely to be present in every individual because the cluster has been defined by variability in the number and severity of the symptoms reported. An increased likelihood (but not certainty) that a group of symptoms will be present concurrently is the only conclusion that can be made. As a result, questions remain about what constitutes a symptom cluster in a clinical population, including how many cluster symptoms must be present and at what level of intensity.

## Symptom Cluster Assessment and Intervention

### Assessment

Little intervention research has addressed interventions for symptom clusters specifically. However, examining the few studies available is instructive. The systematic assessment of multiple symptoms has been examined in at least one study of individuals with advanced cancer (Homsí et al., 2006) in which an open-ended assessment (“What symptoms are you having now?”) was compared with a systematic assessment of 48 symptoms. The median number of symptoms that were



volunteered was only one (range = 0–6); however, the median number of symptoms obtained by systematic assessment was 10 (range = 0–25). The result speaks to the utility of systematic assessment for comprehensive identification of symptoms.

Several studies have tested the efficacy of systematic symptom assessment. A few studies have demonstrated that providing clinicians with systematic assessment information has a beneficial effect on QOL (McLachlan et al., 2001; Sarna, 1998; Taenzer et al., 2000; Velikova et al., 2004) (see Table 2). Sarna pioneered the examination of this technique. Her team compared a structured assessment of 13 symptoms with usual care for 48 newly diagnosed patients with lung cancer. A research nurse conducted the assessment at six consecutive clinic visits and provided a synopsis of the assessment to the clinic nurse at each visit. The group that received the structured assessment had lower symptom distress scores over time than the usual care group. Sarna concluded that systematic assessment of symptoms forestalled an increase in symptom distress.

Several other studies have investigated the use of systematic symptom and QOL assessment, using a computerized QOL scale with results either shared or not shared with healthcare providers. Although one trial was not successful, two others resulted in greater discussion and charting of QOL issues or better overall well-being (McLachlan et al., 2001; Taenzer et al., 2000; Velikova et al., 2004).

## Intervention

Three intervention studies were identified that addressed multiple symptoms (see Table 3). Gaston-Johansson et al. (2000) targeted pain, fatigue, psychological distress, and nausea in patients with breast cancer who underwent autologous bone marrow transplantation (BMT) using a comprehensive coping strategy program that was compared with usual care. The program was administered two weeks prior to hospitalization and reinforced upon admission, two days after chemotherapy, and seven days after BMT. The program was effective in reducing nausea as well as nausea combined with fatigue seven days after BMT, when side effects of treatment were most severe.

Given et al. (2004) used a cognitive-behavioral intervention to reduce symptom severity during chemotherapy for solid tumors; the intervention was compared with usual care. A research nurse assessed 15 symptoms at each contact over the course of 10 contacts. Any symptom rated above the midpoint of the scale received intervention. At the week 10 and 20 observations, a significant interaction occurred between the study group and baseline symptom severity. Patients in the experimental group who had higher symptom severity at

study entry had significantly lower severity at weeks 10 and 20. Participants with worse baseline symptoms had the most benefit from the intervention. Both studies demonstrated benefit from intervention targeted to multiple symptoms.

Intervention for the sickness behavior symptom cluster was evaluated in a small pilot study of 15 patients with advanced lung cancer. Patients were selected for intervention if they presented with a systemic immune-metabolic syndrome (similar to sickness behavior symptoms), including persistent weight loss, anorexia, fatigue, low performance status, and acute-phase protein response (Cerchietti et al., 2004). Intervention consisted of medroxyprogesterone (500 mg twice daily), celecoxib (200 mg twice daily), and oral food supplementation for six weeks. After treatment, 13 of 15 patients had stable weight or weight gain and improvement in weight change ratio. A significant improvement in nausea, early satiety, fatigue, appetite, and performance status also was observed. The findings suggest that patients with advanced lung cancer could benefit from the multitargeted treatment regimen. However, fatigue was the only symptom that was observed and changed; other symptoms (insomnia, pain, and depression) were not evaluated.

Another way to think about intervention for symptom clusters is to consider crossover interventions that have a broad spectrum of effect that can influence more than one symptom (Berger et al., 2005; Carr et al., 2004; Courneya & Friedenreich, 1999; Homsy et al., 2001; Loscalzo, 1996; Mock, 2004; Mock et al., 1997; Pinto & Maruyama, 1999; Pirl, 2004; Sarhill et al., 2001) (see Table 4). For example, the cognitive-behavioral strategy of relaxation has been shown to benefit pain (Loscalzo) and insomnia (Berger et al.). Exercise has demonstrated benefit in relieving fatigue, depression, and insomnia (Berger et al.; Pinto & Maruyama; Stricker, Drake, Hoyer, & Mock, 2004). Antidepressants have been used as adjuvant treatment for pain and insomnia as well as the relief of depression (Berger et al.; Pirl). Psychostimulants have been used to alleviate fatigue and depression (Homsy et al., 2001; Sarhill et al.). However, none of these interventions has been evaluated specifically as a treatment for a symptom cluster.

Currently, some promising research suggests that addressing multiple symptoms is beneficial. Although research evidence is insufficient to provide clear direction for clinical practice, some tentative guidance can be provided. When conducting a symptom assessment, fatigue, insomnia, pain, and depression should be addressed because they have moderate evidence of clustering. However, whether other symptoms should be

**Table 3. Studies of Intervention for Multiple Symptoms**

Study	Sample	Intervention	Results
Cerchietti et al., 2004	15 patients with advanced lung cancer	Medroxyprogesterone 500 mg twice daily, celecoxib 200 mg twice daily, and oral food supplementation for six weeks	Stable weight or weight gain; significant improvements in weight change ratio, nausea, early satiety, fatigue, appetite, and performance status
Gaston-Johansson et al., 2000	180 adults undergoing bone marrow transplantation	Preparatory information, cognitive restructuring, relaxation, and guided imagery versus usual care	Decreased nausea in preparatory information group
Given et al., 2004	237 adults beginning cancer treatment	Symptom information, self-care strategies, communication skills, problem solving, counseling, and support (10 contacts over 20 weeks) versus usual care	Less symptom severity and fewer physical limitations for the symptom intervention group; most beneficial for patients with high symptom severity at baseline

**Table 4. Studies That Examined Crossover Treatments**

Treatment	Pain	Fatigue	Depression	Insomnia
Relaxation	Loscalzo, 1996	—	—	Berger et al., 2005
Exercise	—	Stricker et al., 2004	Stricker et al., 2004	—
Antidepressants	Carr et al., 2004	—	Pirl, 2004	Berger et al., 2005
Psychostimulants	—	Sarhill et al., 2001	Homsy et al., 2001	—

addressed or whether key symptoms exist that must be alleviated to provide overall symptom relief is unknown. For the present, the NCCN guidelines on fatigue (2006b) and distress (2006c) provide algorithms and decision trees for assessment and management.

A great deal of work needs to be done to understand the efficacy of intervention for symptom clusters (Armstrong, 2003; Miaskowski, 2006). Whether the assessment and management of a specific symptom cluster have positive effects on patient outcomes should be evaluated. Also, the so-called crossover treatments should be analyzed specifically to determine their effects on more than one symptom. In addition, testing the mechanisms by which pharmacologic and nonpharmacologic interventions influence symptoms will be necessary.

## Summary

Although research is sufficient to build a case that the symptom cluster has validity as a scientific construct and a clinically relevant problem, many unanswered questions remain, which is why the symptom cluster is described as “elusive.” A great deal of evidence supports the influence of symptoms on one another, and some evidence shows that multiple symptoms affect nursing-sensitive outcomes. Less evidence supports underlying mechanisms or the validity of crossover treatments. Work is needed to operationally define a symptom cluster, understand the basis for the variability of the cluster, standardize its measurement, and identify the most parsimonious strategies to alleviate a symptom cluster. To accomplish this work, developing new tools for studying symptom clusters will be necessary. Working collaboratively to provide full and clear descriptions of the symptom cluster and developing robust yet succinct symptom cluster interventions to achieve the most favorable patient outcomes will be essential.

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