Occurrence of Symptom Clusters

Marylin J. Dodd, Christine Miaskowski, Kathryn A. Lee

Although concurrent symptoms are frequently reported in clinical practice, symptom management research has not reflected this reality. Concurrent, related symptoms, i.e., symptom clusters, are possibly the next generation of work to be done in the area of symptom management. It has been suggested that certain clusters of symptoms may have a synergistic effect on future patient outcomes, and may predict morbidity. The overall goal of this article is to present initial research in the area, along with strategies for development of the concept of symptom clusters. In addition, a working definition of symptom clusters is offered, as well as current issues with the concept and suggestions for future research. [J Natl Cancer Inst Monogr 2004;32:76–8]

To date, the majority of research on symptoms has been directed toward either a single symptom, such as pain or fatigue, or toward their associated symptoms, such as depression or anxiety. Although this approach has advanced the understanding of some symptoms, it is not that helpful to clinicians in guiding practice when the patient presents with several concurrent symptoms.

In response to this lack of knowledge there has been some preliminary work by investigators exploring the occurrence of concurrent, related symptoms and their effect on patient outcomes. Here we describe this initial symptom-cluster research, discuss strategies for concept development of symptom clusters, and suggest a working definition for symptom clusters. In addition, we identify current issues in the area and suggest directions for future research.

BACKGROUND

Recently, it was noted that a cluster of symptoms (pain, fatigue, and insomnia) had a consistent and significant effect on losses in functioning unrelated to patients’ type of cancer treatments, stage of disease, or comorbid conditions in a sample of 826 elderly patients with cancer (1). In consultation with these authors, our team of investigators conducted a secondary analysis of a large data set to determine the effect of the concurrent, related symptoms of pain, fatigue, and sleep disturbance on functional status during three cycles of chemotherapy in a sample of 93 outpatients (2). A hierarchical regression model of our selected symptoms and age explained more than 48% of the variance in functional status (using Karnofsky performance status, KPS). The KPS scores at the beginning of chemotherapy explained 30.8% of the variance in KPS scores three chemotherapy cycles later ($P<.001$). After KPS scores at the beginning of chemotherapy were partialled out from the KPS scores three cycles later, four independent variables entered in the next step were considered predictors of the change in functional status between the two time points. Age explained 11.8% of the change ($P = .001$), pain explained 10.7% ($P = .002$), and fatigue explained 7.3% ($P = .011$). Sleep disturbance was not statistically significant, only explaining 1% of the change ($P = .344$). The symptom cluster did not demonstrate a synergistic effect on the outcome as evidenced by the nonsignificant interactions. With our and others’ findings serving as a base, a search of the literature was conducted for other reports of clusters of symptoms.

A SEARCH OF THE LITERATURE

A thorough search of the cancer literature using the key terms “symptom cluster,” “symptom constellation,” or “symptom combinations” yields one citation (2). The prevalence of coexisting symptoms has been the primary focus of a few data-based articles (3–8). For two or three symptoms to simply occur concurrently (or coexist) is insufficient for them to be labeled a “symptom cluster.” Instead we propose that these symptoms need to be both related to one another and occurring concurrently, such as nausea and vomiting and poor appetite. This requirement is considered an inclusion criteria within the strategy of concept clarification (presented in the next section).

Concurrent symptoms have been used as predictors of subsequent patient outcomes (1,2,4,9) or outcomes themselves (10,11). In several studies, one of the three selected symptoms (pain, fatigue, or depression) was the focus of the investigation, along with other symptoms that were secondary in importance and labeled “correlates” of the primary symptom (5,12,13). We propose that these primary symptoms and their correlates do not qualify (i.e., an exclusion criteria discussed in the next section) as “symptom clusters” (2,14).

Clinical experience suggests that cancer patients experience multiple symptoms. However, the possible “symptom clusters” are buried in the text of articles and in “yet to be analyzed” large symptom data sets, making retrieval and estimates of prevalence difficult to derive. To date, no literature could be found on the occurrence of symptom clusters in children or adolescents, by the stage of cancer, or across the continuum of cancer care (presentation, treatment, survivorship, or palliative care). Only one study could be identified in the literature that had what we would classify as a symptom cluster that included the selected symptoms of pain, fatigue, and depression; this study is discussed next (4).

The purpose of the Gaston-Johansson and associates’ (4) study was to determine the influence of fatigue, pain, and depression on health status in women diagnosed with breast cancer who had completed adjuvant chemotherapy and were awaiting an autologous bone marrow/peripheral blood stem cell transplant. A cross-sectional, correlational design was used with 127 women in the sample who had stages I–IV breast cancer. Participants completed a series of instruments to measure fatigue

Affiliations of authors: Department of Physiological Nursing (MJD, CM), Family Health Care Nursing (KAL), University of California, San Francisco. Correspondence to: Marylin J. Dodd, RN, PhD, FAAN, Box 0610, School of Nursing, University of California, San Francisco, San Francisco, CA 94143-0610 (e-mail: marylin.dodd@nursing.ucsf.edu).

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(Fatigue Visual Analogue Scale), pain (Gaston-Johannson Painometer), depression (Beck’s Depression Inventory), and health perception in general (Medical Outcomes Study Short-Form General Health Survey). The total health perception score is obtained by summing all of the scores of the mental health scales. Ninety-one percent of the participants reported fatigue, 47% reported pain, and 54% reported depression. Fatigue, pain, and depression were all significantly correlated with each other and with total health status. After controlling for demographic variables, depression and sensory pain accounted for 64% of the variance in total health status. Depression and affective pain accounted for 63% of the variance in total health status. Fatigue and depression accounted for 42% of the variance in the perception of health status.

To summarize to this point, no literature could be found on the occurrence of symptom clusters in children or adolescents, by stage of cancer, or across the continuum of cancer care. Only two studies were found that included the symptom of depression as one of the three symptoms in the cluster: Gaston-Johannsen et al. (4), with pain, fatigue, and depression; and Loge et al. (15), with fatigue, anxiety, and depression. There has been some initial research with the concept of clusters of symptoms, although this work is clearly very early in its evolution. Therefore, it is important to consider strategies for concept development. These strategies are presented in the next section.

**CONCEPT DEVELOPMENT**

Concept development is central to the understanding of symptom clusters. The three major strategies for concept development are concept exploration, concept clarification, and concept analysis. Each strategy uses different processes to achieve its goals. The concept of “symptom cluster” is early in its development and is in the phases of concept exploration and concept clarification. Meleis (16, pp. 204–5) defines concept exploration as

... a strategy used when a concept has only recently been introduced in the literature and it is too early to articulate its definite properties and potential explanatory power. ... It is the process by which a phenomenon is identified and introduced to colleagues to raise their consciousness about the phenomenon, to claim its importance and significance, and to stimulate the members of the discipline to consider it further in their research. ... Concept exploration includes identifying the major components and dimensions of the concept with appropriate questions being raised about each component.

In contrast, concept clarification is a strategy of refining existing definitions, considering interrelationships between the different elements of the concept in order to resolve existing conflicts about meaning and definitions. This strategy includes processes of inclusion and exclusion where attempts are made to define what is included and what is excluded in the meaning and attributes of the concept (16). This discussion leads to the next section, that of defining symptom clusters.

**WORKING DEFINITION OF SYMPTOM CLUSTERS**

When three or more concurrent symptoms (e.g., pain, fatigue, and sleep disturbances, or nausea, vomiting, and poor appetite) are related to each other, they are called a symptom cluster (2). The symptoms within a cluster are not required to share the same etiology; for instance, pain may be caused by the cancer, fatigue by the cancer and treatment, and sleep disturbances by selected types of chemotherapy agents or anxiety. Symptom clusters may have an adverse effect on patient outcomes and may have a synergistic effect as a predictor of patient morbidity (2,14).

**Current Issues Related to Symptom Clusters**

Ongoing studies and future research will continue to develop and refine the definition of symptom clusters and their possible effect on patient outcomes. A few selected examples of current issues in the area will be discussed.

Reported low correlations among the symptoms in a cluster with differing etiologies or mechanisms. In the sample of 93 outpatients mentioned earlier, the intercorrelations among the three symptoms of pain, fatigue, and sleep disturbance were low [pain to fatigue, \( r = 0.22, P < .05 \); pain to sleep disturbance, \( r = -0.06, \) nonsignificant; fatigue to sleep disturbance, \( r = 0.13, \) nonsignificant (2)]. Higher and significant intercorrelations were reported by Gaston-Johannsson and associates (4) in their sample of 127 women with breast cancer. Significant correlations were observed between pain and fatigue \( (r = 0.34, P < .001) \), pain and depression \( (r = 0.25, P < .01) \), and depression and fatigue \( (r = 0.58, P < .001) \).

In another sample of 457 Hodgkin’s disease survivors, another cluster of three symptoms with the same (i.e., anxiety and depression measured by the Hospital Anxiety and Depression Scale (HADS) and different etiologies or mechanisms (fatigue measured by Fatigue Questionnaire) correlated moderately (15). Fatigue correlated with anxiety and depression \( (r = 0.44 \) and 0.41, respectively), and anxiety correlated with depression \( (r = 0.63, \) with all correlations reaching statistical significance \( P < .001) \).

In a sample of 164 outpatients, higher correlations were obtained among three symptoms (pain, difficulty eating, and difficulty swallowing) in a cluster with the same etiology; that is, chemotherapy-induced mucositis in a sample of 164 outpatients (17). In this study there were repeated measures of the oral assessments that yielded multiple intercorrelations (Pearson’s correlations) among the symptoms. The symptom of pain correlated with difficulty eating, ranging from 0.60 to 0.71; pain correlated with difficulty swallowing, ranging from 0.43 to 0.50; and difficulty eating correlated with difficulty swallowing, ranging from 0.54 to 0.84. All of the correlations were statistically significant \( P < .001) \).

Is the current requirement (i.e., inclusion criteria) that symptoms be correlated with one another necessary? If the symptoms are not correlated, then this work reverts to summing the frequency of symptoms; this strategy provides only a one-dimensional view of the symptom experience and limits our ability to test for possible synergistic effects on patient outcomes (18).

A related issue of “symptom groupings” in two recent articles. In a study mentioned earlier, Given and her associates (1) studied 826 elderly cancer patients who had received treatment. They documented the number of patients experiencing concurrent pain, fatigue, insomnia, any two of these three symptoms, any one of these three symptoms, and none of these symptoms by cancer type (breast, colon, lung, and prostate). Of the 208 lung cancer patients, 29% experienced all three symptoms, 36% reported two of the three symptoms, 27% reported one of three symptoms, and 8% experienced none of these symptoms. Pain, fatigue, and insomnia were significant and
independent predictors of change in patient functioning (using Medical Outcomes Survey, SF36). These three symptoms had different predictive roles, depending on the site of the cancer. Intercorrelations among the three symptoms were not reported, so their designation as a symptom cluster cannot be made.

In the second study, of 117 outpatients (19), 13.7% reported experiencing all three symptoms (pain, fatigue, and sleep disturbance), 9.4% reported pain and sleep disturbance, 6.8% fatigue and sleep disturbance, 4.3% pain and fatigue, 11.1% only pain, 6.8% only sleep disturbance, 6.0% only fatigue, and 41.9% none of these symptoms. Depression was designated as an outcome variable, and 32% of patients had depressive mood scores (≥16 on the CES-D). Patients who experienced no symptoms had significantly lower depression scores ($F = 13.19, P < .001$), fatigue scores (Lee Fatigue Scale; $F = 21.43, P < .001$), and sleep disturbance scores General Sleep Disturbance Scale ([GSDS]; $F = 52.82, P < .001$) than those patients who experienced two or three symptoms. Patients who experienced only one symptom had a statistically significant lower “worst pain” score than those patients who experienced three symptoms ($F = 6.13, P < .001$). The intercorrelations among the four symptoms were all statistically significant and ranged from 0.30 to 0.57 (Pearson’s correlations). The suggested strength of these relationships in a symptom cluster has not been specified and awaits future research. The correlations between the Performance Status Scores (Karnofsky performance scale) and each of the four symptoms were statistically significant and ranged from −0.36 for the daily “average pain” score to −0.46 for the “worst pain” score.

### Symptom Pairings/Symptom Clusters

Can two concurrent, correlated symptoms constitute a symptom cluster, or is this a “symptom pairing”? This question relates to concept clarification in regard to inclusion criteria (7,20). Is it important whether a symptom cluster is defined as having more than two symptoms, that is, could two symptoms constitute a “cluster”? Does it make a difference? Clearly, given the early development of the concept of symptom clusters, we do not know at the present time. A related final issue is the amount of time that all of the symptoms within the cluster need to be present to be considered a cluster. To date, this time frame is unspecified.

### Areas of Future Research

The synergistic effect of symptoms that constitute a symptom cluster remains to be determined in future research. Other remaining questions include the following: In a cluster of symptoms, the temporal pattern to the symptom that usually is an antecedent to the other symptoms (i.e., which of the symptoms usually occurs first, followed by other symptoms) will need to be determined. Is there a linear relationship between the symptoms in the cluster and their severity? Are the relationships between the three symptoms changed markedly when severity of one of the symptoms is greater? Is the overall health-related outcome changed as well? The answers to these questions and issues presented earlier rest with the many investigators who conduct symptom-focused studies. By including additional study aims and planned data analyses of possible symptom clusters in our ongoing work, our knowledge will be advanced.

### References