Symptom Cluster Research: Conceptual, Design, Measurement, and Analysis Issues

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Abstract:
Cancer patients may experience multiple concurrent symptoms caused by the cancer, cancer treatment, or their combination. The complex relationships between and among symptoms, as well as the clinical antecedents and consequences, have not been well described. This paper examines the literature on cancer symptom clusters focusing on the conceptualization, design, measurement, and analytic issues. The investigation of symptom clustering is in an early stage of testing empirically whether the characteristics defined in the conceptual definition can be observed in cancer patients. Decisions related to study design include sample selection, the timing of symptom measures, and the characteristics of symptom interventions. For self-report symptom measures, decisions include symptom dimensions to evaluate, methods of scaling symptoms, and the time frame of responses. Analytic decisions may focus on the application of factor analysis, cluster analysis, and path models. Studying the complex symptoms of oncology patients will yield increased understanding of the patterns of association, interaction, and synergy of symptoms that produce specific clinical outcomes. It will also provide a scientific basis and new directions for clinical assessment and intervention.
Key Words: Symptoms, symptom clusters, symptom management, quality of life

Article:

INTRODUCTION

Typical symptoms associated with cancer and its treatment include fatigue, nausea-vomiting, pain, depression, and difficulty sleeping. In cancer care, these symptoms can be caused by cancer, cancer treatment, or the combination of cancer and cancer treatment. Despite the knowledge that individuals undergoing cancer therapy are likely to experience multiple concurrent symptoms, most research on symptoms in cancer has examined individual symptoms.[1] The relationship between and among cancer symptoms and the impact on quality of life have not been evaluated systematically. The purpose of this paper is to examine critical research issues related to the conceptualization, design, measurement, and analysis of multiple concurrent symptoms or symptom clusters in oncology.

The Concept of a Symptom Cluster

Recently, Dodd et al .[2] called for consideration of the "symptom cluster" in oncology research to capture the complexity of the cancer symptom experience. The term "symptom cluster" has not

been defined systematically, nor is there an accepted definition in oncology symptom management. The term "symptom" refers to a single subjective indicator of disease or physical disturbance.[3] The term "cluster" suggests the formation of an aggregate of symptoms that are related to each other in a logical or predictable way.[3] Dodd et al.[2,4,5] defined symptom cluster as concurrent and related symptoms that may or may not have a common etiology. Miaskowski et al.[1] have suggested that symptoms can be related through a common mechanism or etiology, by sharing common variance, or by producing different outcomes than individual symptoms.

Only a few theoretical frameworks have addressed the clustering of symptoms. The Symptom Management Model proposed by investigators at the University of California-- San Francisco includes a dimension called the "symptom experience."[2] This dimension comprises the perception, evaluation, and response to symptoms. While the plural term "symptoms" is used, explanations and descriptions in the text refer to the singular "symptom" or "primary symptom." Symptom clusters are referred to as an area for development and refinement of this model. Dodd et al .5 and Miaskowski et al.[1] have further developed the concept of symptom clusters but it has not been addressed in the context of the Symptom Management Model.

A few theorists have described models that are focused on a primary symptom with other symptoms contributing to it. Piper[6] and Winningham et al .[7] have described models of cancer-related fatigue that recognize the impact of other symptoms on fatigue. However, neither of these models addresses the nature of the relationships between fatigue and other symptoms.

Another perspective on symptom clusters describes the "symptom experience," referring to all symptoms "as they are produced and expressed (p. 601)."[8] Lenz's et al.[9] theory of unpleasant symptoms also asserts the presence of multiple symptoms that influence one another. The theory identifies physiological, psychological, and situational antecedents of symptoms as well as functional outcomes of symptoms. This theory describes the nature of the relationships among symptoms as "multiplicative," meaning that two or more symptoms have a catalytic effect on one another. However, this proposition has not been demonstrated empirically. For example, pain could be perceived as considerably worse in the presence of fatigue or nausea; in the presence of both symptoms, pain could be proportionally more severe.

The identification of symptom clusters in medicine and illness care is not new. In fact, from the Middle Ages to the late 19th century, symptoms were generally thought of as the bodily or mental phenomena that constituted specific illnesses.[1] In the 20th century, it became known and accepted that underlying pathophysiologic mechanisms were responsible for the pattern of symptoms that typified different diseases. As the diagnosis of disease became more sophisticated, symptom-based diagnostic criteria were supplanted by laboratory and imaging tests and symptom clusters received less attention.

However, one can observe in recent literature that symptom clusters continue to play a role in the identification and development of diagnostic criteria for some diseases.[1] Diagnostic criteria for some mental illnesses were developed by selecting homogeneous groups of clinical characteristics, primarily symptoms, and defining the diagnosis on the basis of treatment response, family history, and/or specific outcomes.

The diagnosis of many psychiatric syndromes is based on the presence of specific signs and symptoms. For example, the diagnosis of major depression is based on the presence of five symptoms over a 2 week period. [12] One or two sentinel symptoms (depressed mood and/or loss of pleasure in usual activities) must be present plus at least three or four additional symptoms for a total of five symptoms. These may include weight loss or gain, insomnia or hypersomnia, increased or decreased appetite, psychomotor agitation or retardation, fatigue, feelings of worthlessness or guilt, decreased ability to think or concentrate, or recurrent thoughts of death. In addition to the development of clinical diagnostic categories, symptom clusters have been used to explore potential mechanisms of diseases with unknown etiology or pathophysiology.[13,14]

While symptom clusters have been useful in creating diagnostic criteria for many diseases or syndromes, the processes that lead to symptom clusters in oncology are much more complicated. For example, the oncology patient receiving cancer therapy may have some symptoms caused by the disease and others caused by a specific treatment modality, e.g., nausea could result from a tumor obstructing the gastrointestinal tract while fatigue could be due to cancer chemotherapy. A symptom could also be caused by a comorbid condition, for example, pain due to arthritis. A symptom could cause other symptoms; for example, pain could result in sleep disturbances and fatigue. It is also possible that two or more key symptoms could interact resulting in an overall increase in the number of symptoms or functional disturbance. It is possible that a symptom could be a direct cause of one symptom and an indirect cause of another. Symptoms could be related via an underlying physiological or psychological mechanism; symptoms could also coexist without being related. For example, a depressive syndrome has often been proposed as the underlying psychological mechanism of fatigue and insomnia since these symptoms are criteria in the diagnosis of depression.[12] Likewise, cytokine-induced sickness behavior has been proposed as a shared biological mechanism for multiple symptoms such as pain, fatigue, nausea, diarrhea, wasting/cachexia, cognitive impairment, and depression. [15,16]

In oncology symptom management research, the greatest yield from studying a symptom cluster is likely to be increased understanding of the way in which a specific set of symptoms of cancer and its treatment are related, how they influence one another, and how they influence outcomes of interest. While it is important to recognize the common etiology of symptoms when it exists, it is equally important to understand the patterns of association, interaction, and synergy of multiple symptoms that produce specific clinical outcomes. Understanding the complex symptom experience of oncology patients is likely to provide a scientific basis and new directions for clinical assessment and intervention.

Research examining symptom clusters in oncology has been evolving since Dodd et al.[2] made their original challenge to the research community. Research to date reflects an empirical search for common elements among individual symptoms that can link them as members of a symptom cluster. Shared variance, described by Miaskowski et al.[1] as an indicator of symptom clustering, has been examined in numerous studies of correlation between symptom pairs including fatigue-insomnia,[17,18] fatigue- depression,[4,17,19,20] fatigue-pain [41,8,21], and pain-depression. [21] Concurrence and temporal patterning of symptoms have also been explored as indicators of symptom clustering. [22,23] In keeping with the definition, investigators have explored common outcomes related to symptom clusters. Studies have demonstrated that variance in quality of life or functional outcomes can be accounted for by a set of symptoms.[4,21,23] Given and colleagues also

demonstrated that the number of symptoms reported had differential effects on outcomes. In one study,[24] pain and fatigue were independent and additive predictors of co-occurring symptoms. Individuals with both pain and fatigue reported more symptoms overall than those who reported pain or fatigue alone or neither symptom. In a separate study using the same data set, the presence of pain, fatigue, and insomnia together was associated with incrementally greater risk of decreased functioning than the presence of fewer or none of these symptoms. [25]

More recently, the way in which symptoms influence one another has been explored. Beck et al.[26] showed that one symptom can influence another symptom through its effect on a third symptom. The use of a partial mediation model demonstrated that pain influenced fatigue directly as well as indirectly through its effect on sleep. That is, people who were in pain lost sleep resulting in higher levels of fatigue. This model provides information about "how" these symptoms are related to each other.

The investigation of symptom clustering is in an early stage of testing empirically whether the characteristics defined in the conceptual definition can be observed in cancer patients. Continued study of multiple symptoms is necessary to confirm or deny empirically the existence of the symptom cluster. The identification of symptom clusters in oncology patients could yield important information for the assessment and management of symptoms. For example, the identification of key symptom clusters would allow for prioritization of symptoms for assessment and management. An understanding of key symptom clusters would also provide new avenues for interventions to minimize the impact of symptoms on health-related outcomes.

Design Issues in Symptom Cluster Research

As with all research, the challenge of studying symptom clusters is matching the research design to the question or purpose of the study. A cross-sectional design is best used to examine how many people in the population of interest have the symptoms of interest at the time the data are collected. When the symptoms are expected to vary in relation to some other factor, such as time since treatment, the data collection point is standardized based on exposure to the influencing factor. To examine the natural history of a symptom cluster, its pattern over time, or relationships among symptoms over time, a longitudinal design is required.[8]

An important factor in symptom research is the clinical context. While some symptoms are related to cancer, many are specifically related to the treatment that is selected. For example, some forms of therapy are more likely than others to result in nausea/vomiting, neuropathy, flu-like symptoms, skin reactions, or appetite loss. Treatment-related symptoms are likely to appear, peak, and remain or dissipate at predictable times in relation to treatment. In the case of chemotherapy, symptoms such as fatigue, sleep disturbance, and nausea/vomiting increase within 48 hours after treatment, peak at about 96 hours, and dissipate over the course of a cycle of therapy. [27--30] Symptom reports obtained at appropriate times during a chemotherapy cycle are likely to reflect these rapid changes in symptom presence and intensity.

It is important to carefully consider the homogeneity of the sample. Both type and stage of cancer may influence the pattern of symptoms. Symptom patterns also are likely to be influenced by these factors. A symptom cluster for lung-cancer patients is likely to differ from that

experienced by breast-cancer patients.[22,23] It is also likely that the pattern and trajectory of symptoms within a diagnosis will differ for individuals with early- or late-stage disease. It is critical to devise a sampling plan that maximizes access to a homogeneous group of individuals with regard to the symptom cluster of interest.

Another important design issue is the timing of symptom measures.[8] A critical timing decision is whether to examine symptoms in relation to elapsed time (once a month) or landmarks of the treatment experience (number of days after initiation of chemotherapy or radiotherapy). A study of a symptom cluster in a group that has completed all cancer therapy might use the first approach safely. However, the investigator interested in measuring symptoms during treatment would need to select measurement points in relation to treatment landmarks to ensure measurement of symptoms when they occur as well as to avoid events that could confound symptom reports. For example, a measure taken 2 months after diagnosis could vary considerably with regard to phase of treatment. Some individuals could be recovering from surgery, others undergoing chemotherapy, others experiencing a treatment delay, etc. The pattern of symptoms over time would be confounded similarly. Timing by landmarks becomes more complex in the current context of chemotherapy where treatment cycles can vary from weekly to as long as 8 weeks. Innovative approaches to measurement using technology can provide more frequent assessments. [31] This issue will be discussed in greater detail later in this paper.

Another aspect of the clinical context is the availability and use of symptom management strategies that could confound the measurement of symptoms. For example, patients may receive drugs to prevent or alleviate severe symptoms such as pain or nausea. It is essential to keep track of symptom management efforts that could alter the expected severity or pattern of a symptom over time. An alternative would be to exclude individuals receiving therapies that would confound symptom measurement or to collect data frequently enough to capture symptoms when they are most likely to occur, keep track of symptom management efforts, and determine whether or not management was effective.

In symptom cluster research focused on intervention, there are a number of design issues related to the development and implementation of symptom management interventions. It is critical to design appropriate control or comparison conditions so the hypothesis can be tested. For example, a study of a behavioral intervention may benefit from a comparison group that controls for the time and attention of the investigator but does not provide any symptom management. While this may seem self-evident, it is often a challenge to devise a control intervention that has some relevance but is free of active symptom management.

Another issue to consider in an intervention for a symptom cluster is that strategies used to manage or relieve one symptom could exacerbate another. For example, pain and fatigue are two commonly experienced cancer symptoms.[24] A symptom management intervention for pain that involves the use of opioid analgesics is likely to exacerbate the problems of fatigue and constipation. It may be necessary to compromise optimal management of one symptom (such as fatigue) to achieve optimal management of another troubling symptom (such as pain). Such decisions must be made in the context of the goals of the research as well as practical and ethical considerations. More research is needed to address the treatment of a target symptom and its effect on other symptoms.

Another critical issue in the conduct of an intervention for a symptom cluster is the timing of the intervention. An intervention aimed at "preventing" the development of symptoms must be administered before symptoms occur. For individuals who already have symptoms, it is necessary to tailor the intervention so that symptom management instructions are delivered at a time when study participants are able to receive instructions or process information. For example, in a clinical trial of a psycho-educational intervention for fatigue, individuals receiving chemotherapy were not contacted during the 4 days immediately after treatment due to the anticipated intensity of symptoms during that time period.[32]

Measurement Issues in Symptom Cluster Research

The classic conceptualization of a symptom is that it has numerous dimensions. Common dimensions include:

- Timing: onset, duration, and pattern
- Intensity or severity
- Location: localization to specific landmarks or diffuse or systemic
- Distress: the degree to which a symptom bothers an individual
- Exacerbating factors: factors that precipitate or worsen a symptom
- Alleviating factors: factors that reduce or relieve a symptom
- Degree of relief provided by treatments
- Impact: the degree to which the symptom influences activity or function

The presence of so many dimensions for an individual symptom increases the potential complexity of symptom measurement. Thus, it is not surprising that in many cases symptom measurement has been unidimensional, usually focused on severity or distress. Most multi-symptom scales list symptoms and then rate severity and/or distress. The Memorial Symptom Assessment Scale-Short Form asks respondents to check "yes" if they have experienced a symptom within the last week and then to rate "How much did it Distress or Bother you?" on a 5-point rating scale. 33

In contrast, tools developed to measure a specific symptom will usually include multiple dimensions. For example, the Piper Fatigue Scale, [34] the Pittsburgh Sleep Quality Index, [35,36] and the Brief Pain Inventory[37,38] are multidimensional measures of individual symptoms. The Brief Pain Inventory measures pain intensity at its worst, at its least, on average, and now; perceived pain relief; and impact or degree of interference with seven common activities. 39

In the case of a symptom cluster, the easiest approach is to measure one dimension on multiple symptoms. This unidimensional approach to the measurement of multiple symptoms has the advantage of simplicity and low response burden. However, the disadvantage of this approach is that other critical dimensions of the symptom cluster may not be assessed. It must be noted, however, that research has not established the critical dimensions of a symptom cluster that are essential to measure.

A thorough and sound measure of symptom clusters would be multidimensional for multiple symptoms. The researcher could minimize the response burden by including the symptoms that

are most appropriate for a given clinical context; for example, urinary frequency would be an important symptom to measure in men receiving radiation therapy for prostate cancer while dry mouth may not be essential. One way to measure multidimensional symptoms would be by selecting a separate tool for each symptom in the cluster, for example, the Brief Pain Inventory,[38] Pittsburgh Sleep Quality Index, [35] and the Geriatric Depression Scale.[40] This approach, using multiple instruments has the advantage of including all the critical dimensions of each symptom. However, the disadvantages are the complexity of the measures, the use of different methods of scaling responses and time contexts, and higher response burden for study participants.

An alternate approach is to screen for symptom prevalence and then to "drill down" on measuring specific dimensions only on symptoms that are occurring for a specific patient. This approach was used in a study of Telephone-Linked Care in which patients use an interactive voice response telephone communication system to provide daily reports of nine symptoms. [31] This funneling approach to symptom measurement has the advantage of decreasing respondent burden. The disadvantage is an unbalanced data structure as there are no specific data collected when the symptom does not occur, i.e., the participant responds "no" to a screening question.

In addition to dimensionality, a second important decision in symptom measurement relates to the time frame that contextualizes the measure. For example, it is possible to measure current symptoms or symptoms within a specific time period such as today, the past 24 hours, past month, etc. Within this framework, frequency within a certain time frame is sometimes used as a surrogate measure of intensity. For example, the Pittsburgh Sleep Quality Index (1 week version) asks how often during the past week an individual had difficulty sleeping for certain reasons. Responses are "none, one time, two times, or three or more times." Increased frequency is then a measure of poorer sleep quality.

Some tools deliberately measure multiple time frames. The General Fatigue Scale solicits a measure of fatigue severity today, on most days in the past 48 hours, and in the past week .[41,42] This approach has been shown to provide a reliable estimate of symptom intensity. An additional concern regarding timing arises in symptoms that may vary during the course of a day. Thus, a measure which asks about the symptom intensity "at its worst" may not capture the fact that most of the day the symptom was mild and it peaked for a 10 minute period. More complex approaches combining more frequent measures or estimates that are framed by duration (e.g., pain at a moderate level for 2 out of 24 hours) are of increasing interest to symptom researchers.

It is surprising how often the time context is ignored in research designs and tool selection. This issue becomes even more important in symptom cluster research. It may be appropriate to ensure that the time context be consistent across the symptoms of interest. This consistency would especially be true in cross- sectional designs in which factor analysis or cluster analysis was planned. In a longitudinal study planned to test the influence of one symptom upon another or to test mediation models with multiple symptoms, varying time contexts may be appropriate. For example, sleep over the past month may be a predictor of fatigue today.

Given that the concept of a symptom cluster is relatively new to oncology symptom research, it is reasonable to speculate about the characteristics of the ideal measure of a symptom cluster (Table 1). An ideal measure would be consistent in measuring parallel dimensions

Table 1
Ideal Measure of a Symptom Cluster

- Consistent scaling
- Parallel dimensions: severity, distress, etc.
- Consistent time frame
- Consistent clinical context
- Reasonable response burden

of each symptom within the same time frame using the same method of scaling responses to questions. These consistencies would allow for comparisons between symptoms within specific dimensions. For example, it would be possible to compare intensity and distress scores for pain and fatigue measured on the same scale during the same time frame. In addition, the clinical context of measurement would be explicit in the ideal measure. For example, the investigator's interest in fatigue related to cancer chemotherapy or postsurgical pain would be made explicit in the measure. Lastly, the ideal measure would be designed to maintain a reasonable response burden for study participants.

In a recent large national trial of individuals with cancer who had completed radiation therapy, Mooney et al .31 attempted such an approach. Using a Computer-Assisted Telephone Interviewing system, each patient was systematically screened as to whether he or she had experienced a certain symptom during radiation therapy (the clinical context and time frame). Symptoms included pain, nausea, fatigue, anxiety, feeling blue, decreased appetite, and fever or infection. Additional symptoms that were relevant for subgroups of patients (sore mouth, shortness of breath, urinary burning, and diarrhea) were added depending on the radiation site. For each symptom identified by the patient, specific dimensions were measured including severity, distress, duration, and relief provided.[31]

As the process of measurement becomes more complicated in the case of symptom clusters, it is important to consider the use of technology. Touch-screen computers, hand-held devices, and automated telephone reporting could allow for more frequent and more accurate reporting of symptoms than a paper questionnaire or symptom journal. In addition to the example provided of Telephone-Linked Care using interactive voice response, [31] others have set up computer kiosks to assess symptoms in clinical settings[43] or used palm pilots to gather frequent symptom data using a technique called ecological momentary assessment.[44] Measurement devices such as the use of actigraphy, a small watch-like motion detector, can be used to reliably measure length and patterns of sleep/rest.[45] As the integration of computer and telecommunications technology continues, cellular phones or watch-sized computers will also be available for collecting symptom data.

The Analysis of Symptom Clusters

A number of analytic approaches have been used to examine symptom clusters; however, "best" practice with regard to analysis has not been established. Perhaps the most common approach to grouping symptoms is factor analysis, which examines the relationships among a number of

variables (e.g., symptoms severities) based on the matrix of correlation coefficients between the variables.[46,47] Factor analysis is used to predict a set of latent factors that are responsible for covariance among a group of symptoms. Symptoms due to this latent factor would covary more strongly with each other than they would with symptoms that are affected by a different latent factor. This covariance can be examined using a general factor model or principle components analysis.[47] A benefit of the principle component analysis is that it can yield principle component scores, which reduce several items to a single weighted score for use in other parametric analyses such as test of group differences.

Until recently, there has been no research using this approach to examine symptom clusters in cancer patients, although the procedure has been used widely to examine symptom clusters related to other chronic diseases.[48--50] In a recent study of symptom clusters in lung-cancer patients, Gift et al.[23] used an exploratory maximum likelihood factor analysis of a 32-item scale measuring symptom occurrence and severity to identify a symptom cluster that included fatigue, nausea, weakness, appetite loss, altered taste, and vomiting. A four-factor solution for symptom occurrence accounted for 31% of the item variance. The first factor displayed item loadings higher than 0.4 for the six symptoms in the cluster.

Cluster analysis is another procedure that can be used to define a symptom cluster. Cluster analysis is an exploratory technique that it is used to "discover" underlying groups of individuals who are similar in their symptom experience or symptom profile. Although this approach to data analysis has not been used to examine symptom clusters in cancer patients, it is widely used to examine symptom patterns in other chronically ill populations. [50,51]

There is an inherent appeal for the use of cluster analysis in the study of symptom clusters. Whereas factor analysis groups symptoms into similar groupings (factors), cluster analysis groups individuals into mutually exclusive subsets of individuals with similar profiles of symptoms. [52,53] Cluster analysis could be useful clinically to identify subgroups of individuals who have a distinctive profile of symptoms allowing clinicians to target specific interventions to each subgroup.

Factor analysis and cluster analysis can be used to discover the underlying structure of symptoms or the underlying groupings of patients with similar symptom profiles. Factor analysis is well known for its use in the construction of psychometrically sound scales. A scale is typically constructed around the latent factors discovered in the analyses. For instance, symptoms could factor into two scales comprised of somatic and psychological factors. These scales could be used in parametric analyses to examine correlates (antecedents or consequences).

Geisser et al.[51] used cluster analysis to examine responses of chronic pain patients to the Brief Symptom Inventory,[54] a brief measure of psycho-pathology. The results demonstrated two distinct subgroups. Cluster 1 included individuals with low distress on all Brief Symptom Inventory (BSI) subscales; Cluster 2 included individuals with high distress. The two cluster groups differed with regard to demographic and clinical characteristics: the high- distress group reported worse pain intensity, greater disability, and lower satisfaction with medical care; they were also more likely to be divorced or separated, less able to work, and more likely to be engaged in litigation. Distinguishing high- and low-distress groups would allow for more

efficient treatment planning, using conventional pain management services for the low-distress group and multidisciplinary approaches with the high-distress group.

Both factor analysis and cluster analysis methods are exploratory and descriptive, examining the underlying structure of a group of symptoms (factor analysis) or the clustering of individuals with similar symptom patterns (cluster analysis). However, it is possible to examine the processes by which symptoms influence one another using path models. [55,56] It is possible that one symptom could influence another symptom through its relationship to a third symptom or factor. Path models allow for the examination of both direct and indirect relationships among variables such as a group of symptoms. Regression techniques, path analysis models, and structural equation modeling can be used to examine direct and indirect effects of variables. [55]

Examining direct and indirect relationships can be very beneficial in understanding how symptoms influence one another. In an earlier work that can be thought of as a study of symptom clusters, Williamson and Schulz [57] noted that the relationship between pain and depression in cancer patients was consistent with work in other chronic disease. In general, pain is positively correlated with depression. Thus, one could term pain and depression as a sym - tom cluster. However, Williamson and Schulz[57] focused on an explanatory model for how pain was related to depression. Mediation modeling was used [58] to uncover the relationship between pain and depression. Regression analysis demonstrated that the symptom of pain was indirectly related to depression through its relationship with functional impairment. The relationship between the two symptoms was mediated by impaired functioning in usual activities. That is, individuals with impaired functioning due to pain had more depressive symptoms than those with less functional impairment.

Similarly, Bennett et al.[59] noted that the association between medical diagnoses and functional limitations, while well-documented, was of little use in intervention planning. Using path analysis, they demonstrated that the adverse effect of medical conditions on functioning was mediated by symptoms. Individuals with the symptoms of pain and fatigue due to their medical conditions had worse functional impairment. This result focuses attention on modifiable symptoms for intervention rather than chronic illnesses that are less modifiable.

Summary

Multiple symptoms in cancer patients present a complicated pattern of relationships. The current challenge is to demonstrate convincingly the presence and utility of the construct of a symptom cluster. Another challenge is to address confounding factors in the research design. The sampling plan should control for cancer diagnosis and stage of disease as well as the type of cancer treat- ment. Symptom measurement should be timed to the landmarks of the disease and treatment process. Palliative management of symptoms should be accounted for. An ideal symptom cluster measure includes parallel dimensions of each symptom within the same time frame using the same method of scaling responses to questions. For intervention studies, intervention development should focus on optimal management of all symptoms in the cluster. Analytic methods can include factor analysis to determine the underlying structure of a group of symptoms, cluster analysis to define group of individuals with similar symptom patterns, and path models to examine direct and indirect relationships among symptoms. Continued study of multiple symptoms will yield empirical confirmation or denial of the existence of symptom

clusters. It will also yield increased understanding of the patterns of association, interaction, and synergy of multiple symptoms that produce specific clinical outcomes. Understanding the complex symptom experience of oncology patients will provide a scientific basis and new directions for clinical assessment and intervention.

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