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Title

Advancing Symptom Science Through Symptom Cluster Research: Expert Panel Proceedings and Recommendations.

Permalink

<https://escholarship.org/uc/item/8c91m5q9>

Journal

Journal of the National Cancer Institute, 109(4)

ISSN

0027-8874

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Publication Date

2017-04-01

DOI

10.1093/jnci/djw253

Peer reviewed

REVIEW

Advancing Symptom Science Through Symptom Cluster Research: Expert Panel Proceedings and Recommendations

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Abstract

An overview of proceedings, findings, and recommendations from the workshop on “Advancing Symptom Science Through Symptom Cluster Research” sponsored by the National Institute of Nursing Research (NINR) and the Office of Rare Diseases Research, National Center for Advancing Translational Sciences, is presented. This workshop engaged an expert panel in an evidenced-based discussion regarding the state of the science of symptom clusters in chronic conditions including cancer and other rare diseases. An interdisciplinary working group from the extramural research community representing nursing, medicine, oncology, psychology, and bioinformatics was convened at the National Institutes of Health. Based on expertise, members were divided into teams to address key areas: defining characteristics of symptom clusters, priority symptom clusters and underlying mechanisms, measurement issues, targeted interventions, and new analytic strategies. For each area, the evidence was synthesized, limitations and gaps identified, and recommendations for future research delineated. The majority of findings in each area were from studies of oncology patients. However, increasing evidence suggests that symptom clusters occur in patients with other chronic conditions (eg, pulmonary, cardiac, and end-stage renal disease). Nonetheless, symptom cluster research is extremely limited and scientists are just beginning to understand how to investigate symptom clusters by developing frameworks and new methods and approaches. With a focus on personalized care, an understanding of individual susceptibility to symptoms and whether a “driving” symptom exists that triggers other symptoms in the cluster is needed. Also, research aimed at identifying the mechanisms that underlie symptom clusters is essential to developing targeted interventions.

Patients with chronic conditions, such as cancer and other rare diseases, experience an array of multiple co-occurring symptoms (eg, pain, fatigue, sleep disturbance). When these symptoms remain underdiagnosed and undertreated, they have a negative impact on patient-reported outcomes (PROs) including functional performance, cognitive status, and quality of life

(QOL). A reduction in symptom burden in these patients has the potential to improve their capacity to live well over their entire lives. To achieve this goal, a transformation is needed in how multiple co-occurring symptoms are assessed and managed in order to improve patient outcomes and stimulate a reduction in health care utilization and costs. A strategic plan that advances

Table 1. Characteristics of a symptom vs a symptom cluster

Symptom*	Symptom cluster
	Same characteristics as a symptom—plus:
Subjective perception	Two or more concurrent symptoms
May vary over time	Stable group of symptoms
Has antecedents	Independent of other clusters
Influences outcomes	May have shared underlying mechanism(s)
May be influenced by an intervention	May have shared outcome(s)
Has an underlying mechanism	Temporal dimension

*Symptoms are subjective sensations. Signs are objective indications of some medical characteristic.

symptom science through symptom cluster research has the potential to accelerate the growth of an empiric body of knowledge that is capable of sustaining innovative symptom management interventions in these patients.

While research often focuses on a single symptom, in cancer and most other chronic conditions, patients experience multiple co-occurring symptoms that are related to each other (ie, symptom clusters) (see Table 1). Compared with a single symptom, the occurrence of symptom clusters appears to worsen patient outcomes. For example, in several studies (1–3), the symptom cluster of pain, fatigue, sleep disturbance, and mood disturbance resulted in statistically significant decrements in patients' functional status and QOL. In addition, a limited amount of evidence suggests that treatments for one symptom may "cross-over" and reduce the severity of other symptoms included in a "cluster" (4). This complex relationship between and among symptoms within a cluster may provide new targets for interventions to reduce the negative impact of multiple co-occurring symptoms on patient outcomes.

Symptom science is an identified theme in the National Institute of Nursing Research's (NINR) strategic plan, as well as an important component of the science that is supported by NINR's intramural and extramural programs. Great emphasis is placed on enhancing symptom science because multiple co-occurring symptoms are highly prevalent in patients with cancer, as well as the most common chronic conditions. This interest in the concept of symptom clusters began about 15 years ago and is particularly meaningful for clinicians who seldom assess patients who have a single symptom. While the psychiatric literature provides excellent examples of the use of hierarchical cluster analysis to define subgroups of patients within a diagnostic subgroup (for examples, see 5–7) or as diagnostic criteria (for examples, see 8,9), the majority of the research on symptom clusters in patients with chronic conditions was conducted with oncology patients. However, an emerging body of evidence suggests that symptom clusters occur in patients with a variety of chronic conditions (eg, HIV disease [10,11], chronic obstructive pulmonary disease [COPD] [12,13], heart disease [14], end-stage renal disease [ESRD] [15,16]). Nonetheless, research on symptom clusters is extremely limited. Scientists are just beginning to learn how to study symptom clusters and are developing comprehensive frameworks and applying new methods and approaches to investigate this concept.

To advance the evolving research fields of symptom clusters, symptom science, and personalized strategies for symptom management in rare diseases, the NINR and the Office of Rare

Diseases Research, National Center for Advancing Translational Sciences, sponsored a workshop entitled "Advancing Symptom Science Through Symptom Cluster Research" in June 2015 at the Bethesda campus of the National Institutes of Health. The purpose of this workshop was to engage an expert panel in an evidenced-based discussion regarding the state of the science related to symptom clusters in chronic conditions that included rare diseases and rare cancers. The Rare Diseases Act of 2002 defined a rare disease as one that is diagnosed in fewer than 200 000 people per year in the United States. For rare cancers, this definition translates to fewer than 15 cases per 100 000 per year. Rare cancers include almost every type, with the exception of breast (women or familial), lung, prostate, and skin cancers (basal and squamous cell). Some of the most common cancers such as kidney, non-Hodgkin's lymphoma, and colorectal are considered rare diseases, as are all childhood cancers.

Based on their expertise, panel members were divided into teams to address five key areas: 1) defining characteristics of symptom clusters, 2) priority symptom clusters and underlying mechanisms, 3) measurement of symptom clusters, 4) targeted interventions for symptom clusters, and 5) new analytic strategies for symptom cluster research. Each team 1) was provided with a set of questions to guide their work (see the [Supplementary Material](#), available online) and was asked to prepare a two-page summary that synthesized the state of the science related to their topic, 2) identified limitations and gaps in the current literature, 3) commented on the transferability of the concept of symptom clusters to chronic conditions other than cancer, and 4) identified directions for future research. At a face-to-face meeting, in-depth discussions of each key area occurred and consensus was reached on critical gaps and strategic opportunities for research in each of the key areas. The purpose of this paper is to summarize the findings from this meeting and to provide the initial structure for a transformative blueprint to guide forthcoming research on symptom clusters in patients with cancer, other chronic conditions, and rare diseases.

Defining Characteristics of Symptom Clusters

State of the Science

Following the challenge from the Symptom Management Research Group at the University of California, San Francisco, to the scientific community to consider the concept of a "symptom cluster" (17) and the publication of a state of the science lecture on symptom cluster research in oncology patients (18), a number of review articles have examined the conceptual and methodological issues associated with defining the characteristics of a symptom cluster (19–28). Three topics were the foci for the discussion of the "state of the science" in the area of defining characteristics of symptom clusters, namely conceptual issues, empiric identification of symptom clusters, and changes in symptom clusters over time.

Conceptual Issues

From a conceptual perspective, Brant and colleagues noted that two models (29,30) and two theories (31,32) have incorporated the concept of a symptom cluster (33). Across these four symptom management theories or models, the concept of a symptom cluster is discussed, contextual or antecedent variables are identified, and the potential impact of symptom clusters on patient outcomes is addressed. One of the major limitations of all

of these models is the lack of specificity in how to evaluate the temporal component (ie, if and how symptom clusters change over time). At the conclusion of their review (33), Brant and colleagues created a symptom cluster model that incorporated a temporal dimension using multivariable statistical constructs.

While the definition of a symptom cluster is evolving, panel members proposed, based on the existing evidence, a structure to compare the characteristics of a symptom with a symptom cluster (see Table 1). From a conceptual perspective, the defining characteristics of a symptom cluster should include the patient's symptom experience, temporal characteristics of the symptoms within a cluster, and phenotypic and molecular mechanisms associated with symptoms within the cluster.

Identification of Symptom Clusters

Symptom clusters have been identified in patients with a variety of chronic conditions using “de novo” or “a priori” methods (28). For example, using qualitative research methods (34–37), several groups of interlinked symptoms were identified de novo through interviews with oncology patients. In several quantitative studies (38–42), a variety of statistical approaches (eg, factor analysis [FA], hierarchical cluster analysis [HCA], principal components analysis [PCA]) were used to identify symptom clusters de novo. The outcome of these types of analyses is the de novo identification of one or more symptom clusters, each of which contains two or more symptoms.

In the alternative approach (ie, the a priori identification of a symptom cluster), investigators prespecify the symptom cluster of interest, usually based on some empiric evidence of a relationship among the symptoms. For those studies that used an a priori symptom cluster, the outcome was the identification of subgroups of cancer patients with similar symptom experiences using grouping techniques such as severity of symptoms (43), HCA (1), and latent class analysis (LCA) (3). For example, in a study of patients with lung cancer that identified patients based on the magnitude of fatigue, pain, dyspnea, and insomnia (43), three groups were identified (ie, mild, moderate, severe). In two studies of patients with breast cancer, different statistical procedures were used to identify patient subgroups based on slightly different prespecified symptom clusters. In the first study, which evaluated a psycho-neurological symptom cluster (ie, fatigue, insomnia, pain, depressed mood, and cognitive disturbance) (1) using HCA, four groups were identified and named: all low symptoms, all high symptoms, low pain–high fatigue, and high pain. In the second study that evaluated the symptom cluster of pain, fatigue, insomnia, and depression (3) using LCA, three groups of breast cancer patients were identified (ie, all low symptoms, all high symptoms, and low pain–high fatigue).

Several reviews have evaluated for consistency in symptom clusters identified de novo across studies and populations (25–27). Across these reviews, it is evident that little consistency exists in the number and types of symptom clusters identified. For example, in a review of eight studies of patients with metastatic cancer (27) and another review of five studies of patients with breast cancer (25), no consistency was found in the number or types of symptom clusters. In addition, in a review of the gastrointestinal symptom cluster in oncology patients (26), of the 40 clusters identified across the studies evaluated, 38 clusters included different combinations of co-occurring symptoms. Finally in a review of five studies of symptom clusters in patients with lung cancer (24), only a nausea/vomiting and a respiratory cluster were common across two of the studies.

Changes in Symptom Clusters Over Time

A limited amount of evidence suggests that the number and composition of symptom clusters remain relatively stable over time. For example, in a study that evaluated symptom clusters at the middle, end, and one month after radiotherapy for breast or prostate cancer (44), four relatively similar symptom clusters were identified across the three time points (ie, mood-cognitive, treatment-related, sickness-behavior, and pain). In a study of breast cancer patients undergoing treatment (38), a psycho-neurological symptom cluster was identified prior to treatment and during treatment. In contrast, in a sample of patients with ovarian cancer being treated with chemotherapy (39), the number and type of symptom clusters varied over time.

Transferability to Other Chronic Conditions

Research on symptom clusters in noncancer chronic conditions and in the setting of co-existing chronic illness and cancer is in its infancy. Some data are available on symptom clusters in patients with HIV disease (10,11), chronic kidney failure and end-stage renal disease (15,16), COPD (12,13), osteoarthritis (45), rheumatoid arthritis (46), and heart failure (14). Similar to studies in oncology, the occurrence of symptom clusters in these chronic conditions is associated with decrements in functional status and QOL, as well as increased health care utilization and mortality. Key questions that remain to be answered are the similarities and differences in number and types of symptom clusters, associated risk factors, underlying mechanisms, and effective treatments across these chronic conditions. In addition, in patients with cancer and other chronic conditions, studies of changes in symptom clusters in relationship to patients' disease status (eg, prior to, during, and following an intervention, at different stages of the disease trajectory) are warranted.

Future Directions

While advances have been made in the conceptualization and evaluation of symptom clusters using various analytic techniques, a number of areas warrant investigation to advance the field of symptom cluster research. As noted by Miaskowski (28), three areas warrant additional consideration: conceptual issues, the empiric or de novo identification of symptom clusters, and the identification of patient subgroups based on their experiences with a specific symptom cluster. Some of the opportunities identified by the panel for future research in this key area are summarized in Box 1.

Priority Symptom Clusters and Underlying Mechanisms

State of the Science

Two topics were the foci for the discussion of the “state of the science” in the area of priority symptom clusters and underlying mechanisms, namely priority symptom clusters and mechanistic considerations. During the meeting, the concept of a priority symptom cluster was discussed in terms of the identification of the “sentinel,” “most important,” and/or “most common” symptom cluster within the context of two or more symptom clusters being identified de novo. As Barsevick noted in her state of the science paper (47), the identification of the

Box 1. Directions for future symptom cluster research in each key area

1) Defining characteristics of symptom clusters

Establish a common conceptual framework and approach for the evaluation of measurement of symptom clusters (eg, number of symptoms, dimensions of the symptom that are evaluated, temporal characteristics of symptom clusters)

Determine the specific characteristics that define a symptom cluster

Create an operational definition for a symptom cluster

Determine the sentinel symptom within a symptom cluster

Evaluate the linkages between signs (objective indications of some medical characteristic) and symptoms (subjective sensations) within a cluster

Evaluate for symptom clusters in defined patient subgroups

Develop qualitative approaches to identify symptom clusters and prioritize them by their importance to patients

Develop a methodological primer with common standards for conducting symptom clusters research

Develop a consistent approach to identify subgroups of patients based on a prespecified symptom cluster

Identify, within and across the most common chronic conditions, the most common symptom clusters “de novo”

Replicate studies of subgroups of patients with the same and different experiences with a prespecified symptom cluster; tailor assessment, interventions, and outcome measurements to evolving symptom clusters over the disease trajectory

Determine the phenotypic and molecular predictors of and/or risk factors for the development of prespecified symptom cluster in patients with different chronic conditions

Evaluate the potential to use large data sets and the electronic health record to evaluate symptom clusters

Develop and test methods to evaluate symptom clusters in patients who cannot self-report symptoms (eg, patients with dementia)

Develop and test methods to evaluate symptom clusters using proxy (eg, clinician, family caregivers) reports of symptoms

2) Underlying mechanisms and priority symptom clusters

Develop a core set of symptom inventories for symptom clusters research

Compare and contrast the number and types of symptom clusters across the most common chronic conditions (eg, cancer, heart failure, diabetes, chronic obstructive pulmonary disease)

Evaluate the mechanisms that underlie symptom clusters, including but not limited to: 1) inflammation/immune system, 2) sympathetic nervous system activation, 3) hypothalamic-pituitary-adrenal axis activation, and 4) changes in the central nervous system

Determine the best approaches to evaluate the underlying genetic and epigenetic mechanisms for symptom clusters

Determine the best methods to evaluate the biobehavioral mechanisms for symptom clusters

Develop and evaluate animal models of symptom clusters

Determine if common mechanisms exist across symptom clusters

Develop a systematic approach for the selection of biomarkers for symptom cluster research

3) Measurement of symptom clusters

Use qualitative methods to identify generic and disease-specific symptom clusters across common chronic conditions

Use mixed methods approaches to identify generic and disease-specific symptom clusters across common chronic conditions

Develop common and disease-specific measures to evaluate symptom clusters within and across common chronic conditions

Determine the optimal approach to data collection for symptom cluster research

Compare and contrast the number and types of symptom clusters identified in patients with common medical conditions using a variety of analytic techniques

Compare and contrast changes over time in the number and types of symptom clusters within and across common chronic conditions using a variety of analytic techniques

Evaluate the validity, reliability, and responsiveness of PROMIS measures in symptom cluster research

Build a common core data set for pooling data and assessing data comparability across symptom cluster studies

Use new methods to refine measures for symptom cluster research (eg, Rasch analysis)

Establish red flag values for symptom clusters that warrant intervention(s)

Correlate various outcomes from symptom clusters (eg, functional status, quality of life, mortality, costs, health care utilization, patient satisfaction, caregiver burden, work productivity, absenteeism)

Evaluate symptom clusters in pediatric patients with a variety of chronic conditions

4) Targeted interventions

Evaluate the use of new trial designs (eg, MOST, SMART) to determine whether they can be used to tailor interventions to treat single or multiple symptoms within a symptom cluster

Determine the most efficacious interventions for various symptom clusters

Determine the most appropriate outcome for symptom cluster intervention study

Evaluate the use of technology in symptom cluster research

5) New analytic strategies

Apply new analytic techniques to symptom cluster research (eg, evolutionary algorithms, latent transition analysis, machine learning, risk stratification)

Establish guidelines for choosing the optimal analytic strategies for symptom cluster research

priority symptom cluster may be useful to guide the development of interventions for symptom clusters.

Priority Symptom Clusters

A search of the Cumulative Index of Nursing and Allied Health Literature (CINAHL), PubMed, and EMBASE databases identified 158 papers that used some analytic technique to identify symptom clusters. Across this literature, the papers were divided into those that evaluated symptom clusters associated with a chronic condition (eg, cancer) or its treatment (eg, chemotherapy, radiation therapy) or those that evaluated heterogeneous samples in terms of a variety of chronic conditions or treatments. Across all of the literature evaluated, the three most common symptom clusters identified were: 1) a fatigue, pain, depression, and sleep disturbance cluster, with three of these four symptoms present in 49% of the studies; 2) a gastrointestinal cluster that consisted of nausea and vomiting or only nausea in 21% of the studies; and 3) an anxiety and depression cluster in 21% of the studies. The majority of these studies (~83%) evaluated co-occurring symptoms in patients with cancer.

Mechanistic Considerations

A search of the PubMed, CINAHL, and PsycINFO databases from January 1990 to May 2015 identified only 11 papers that addressed the underlying mechanisms for symptom clusters. In 10 of these papers (2,3,48–55), patients with cancer were evaluated. In the 11th paper (56), elderly individuals with impaired cardiac function or heart failure were evaluated. Nine of 11 papers discussed the mechanisms underlying a single symptom cluster. However, the specific symptoms within the prespecified symptom cluster were somewhat variable and included fatigue, pain, and depression (five papers: 48–50,53,54); fatigue, pain, depression, and sleep disturbance (three papers: 2,3,52); and fatigue, depression, and sleep disturbance (one paper: 56). The other two papers discussed the underlying mechanisms for multiple co-occurring symptoms without specifying a specific symptom cluster (51,55).

The primary mechanisms that were evaluated or discussed included cytokines and inflammation (eight papers: 2,3,49–52,55,56); immune responses (two papers: one on eosinophils [53] and one on viral antibody [48]); activation of the sympathetic nervous system and activation of the hypothalamic-pituitary-adrenal (HPA) axis (one paper: 54). Findings on the involvement of each of these four mechanisms in the development of symptom clusters are summarized below.

Of the eight studies that evaluated cytokines and inflammation, four of them evaluated for differences in cytokine gene polymorphisms in subgroups of patients with different experiences with a prespecified symptom cluster (eg, low symptom burden vs a high symptom burden) (2,3,50,51). In all four of these studies, associations were found between single-nucleotide polymorphisms (SNPs) in inflammatory genes (eg, interleukin 6 [IL6], IL13, tumor necrosis factor [TNF] alpha, IL4, IL1B, TNFR2, PTGS2, and IL10RB) and a higher symptom burden. In four studies that evaluated associations between inflammatory cytokine levels and a psychoneurological symptom cluster, C-reactive protein (CRP) (56), IL4, IL5, IL6, IL7 (52) and sTNF-R1, and IL6 (55) were associated with a higher symptom burden. However, CRP was not statistically significant in one study (49).

In terms of other types of immune responses, in a study of 206 patients with hepatobiliary cancer (53), higher levels of pain, fatigue, and depression were associated with higher eosinophil counts at three and six months after treatment. However, in the multivariable model, only pain was statistically

significantly associated with elevated eosinophil counts. In another study of breast cancer survivors ($n = 200$) (48), patients who were lonelier had higher cytomegalovirus (CMV) antibody titers, which, in turn, was associated with higher levels of the symptom cluster of pain, depression, and fatigue.

In terms of the sympathetic nervous system (evaluated using plasma levels of cortisol and adrenocorticotrophic hormone) and the HPA axis (evaluated using plasma levels of epinephrine and norepinephrine), only one study was identified that evaluated patients with advanced cancer ($n = 104$). In this study (54), higher levels of neuroendocrine markers were associated with the symptom cluster of fatigue, depression, and pain.

Transferability to Other Chronic Conditions

Given the findings reported to date, it is not entirely clear whether the same number and types of symptom clusters will be identified across all chronic conditions. It is conceivable that some symptom clusters will be “generic” across chronic conditions. Other clusters may vary by chronic condition or by treatment modalities within chronic conditions. A similar hypothesis could be made for the underlying molecular and/or behavioral mechanisms for symptom clusters within and across chronic conditions.

Future Directions

In order to identify common, unique, and most important symptom clusters across chronic conditions, as well as their underlying mechanisms, several areas warrant consideration. Consensus is required on how symptoms are measured (eg, unidimensional vs multidimensional instruments), how data are collected (eg, cross-sectional vs longitudinal), and which analytic approaches are used to identify symptom clusters (eg, cluster analysis, factor analysis). An additional consideration is to identify clearly if symptom clusters are being created *de novo* or if subgroups of patients with a prespecified symptom cluster are being evaluated (ie, a priori identification of a symptom cluster) (28). In terms of the identification of the molecular and/or behavioral mechanisms that underlie symptom clusters, studies are extremely limited and findings warrant replication in patients with cancer and other chronic conditions. Some of the opportunities identified by the panel for future research in this key area are listed in Box 1.

Measurement of Symptom Clusters

Two topics were the foci for the discussion of the “state of the science” in the area of measurement of symptom clusters, namely accurate measurement of symptom clusters and analytic strategies that can be used to identify symptom clusters.

Accurate Measurement of Symptom Clusters

While the measurement of symptoms is critical to the determination of symptom clusters, the systematic evaluation of symptom clusters is in its infancy. At this point in time, no “gold standard” assessment tool is available to evaluate symptom clusters in patients with chronic conditions. In addition, it is not clear which dimension of a patient’s symptom experience (ie, occurrence, severity, distress) should be used to create symptom clusters *de novo*.

In a systematic review of cancer symptom assessment instruments (57), 21 instruments were identified as appropriate for clinical use. However, these instruments varied in terms of the number of symptoms assessed, the symptom dimensions that were evaluated, the rating scales used to assess symptom dimensions (eg, 0 to 10 numeric rating scale (NRS), Likert scale), and the recall period for symptom assessment (eg, now, past week). In addition, the psychometric validation of these instruments was highly variable. Given that studies of multiple co-occurring symptoms in oncology patients found that patients report an average of 10 symptoms regardless of their specific cancer diagnosis, stage of disease, or type of treatment (58–61), a symptom assessment instrument that evaluates the most commonly occurring symptoms in oncology patients and in patients with other chronic conditions is necessary to perform symptom cluster research.

An additional point that warrants consideration, particularly in terms of evaluating the generalizability of symptom clusters, is whether a “core” set of symptoms should be evaluated across all chronic conditions. Equally important is whether disease-specific symptoms (eg, specific symptoms for patients with heart failure, ESRD, COPD, various cancer diagnoses) should be added to the core set of symptoms to be able to identify symptom clusters that are common across chronic conditions, as well as symptom clusters that are unique to patients with a particular chronic condition. For example, in oncology research, instruments like the Memorial Symptom Assessment Scale (62), the MD Anderson Symptom Inventory (63), or the Rotterdam Symptom Checklist (64) have identified a number of “generic” symptom clusters (eg, a sickness behavior symptom cluster, a gastrointestinal symptom cluster), as well as disease- (eg, differences in symptom clusters between patients with breast and prostate cancer) and treatment-specific symptom clusters (eg, skin changes associated with radiation therapy).

Another area for consideration is how to optimize the collection of symptom data in order to evaluate symptom clusters in patients with chronic conditions. In most studies of oncology patients (38,65), self-report questionnaires were completed using a paper-and-pencil format or a tablet computer. The time to complete an instrument depended on the number of symptoms and the dimensions of the symptom experience that were assessed. Consideration needs to be given to the optimal methods to use to collect symptom data (eg, smart phone) to be able to determine whether symptom clusters change in patients with a variety of chronic conditions.

Qualitative methods can be used to gain important insights into the types of symptom clusters that patients experience as a result of a chronic condition. Qualitative research may provide meaningful data on how patients view, prioritize, and evaluate symptom clusters; may lead to the identification of new symptoms and symptom clusters as new therapies are introduced; and may determine how the occurrence of symptom clusters influences patients' adherence with their treatment regimen and associated outcomes (eg, functional status, cognitive status, QOL).

Analytic Strategies to Use to Identify Symptom Clusters

In an excellent review (20), Skerman and colleagues examined the conceptual and contextual appropriateness of the most commonly used multivariable methods to identify symptom clusters (ie, cluster analysis, factor analysis). While both methods capture the key attributes of a symptom cluster (ie, related and concurrent symptoms), they differ both conceptually and

mathematically and are relevant in different contexts. For example, if the symptoms in a cluster co-occur but are etiologically independent, then either cluster analysis or factor analysis can be used to identify a symptom cluster. However, if the symptoms are related because they share a common etiology, then factor analysis is the appropriate analytic method because the underlying concept in factor analysis is that the observed variables (eg, nausea, vomiting, weight loss, changes in the way food tastes) are indicators of some unobserved factor (eg, chemotherapy-related symptom cluster). In cluster analysis, similar symptoms are assigned to groups based on the proximity of ratings or similar response patterns (correlations) across individuals, and underlying constructs are not considered in this analytic technique.

For the majority of oncology studies, factor analytic techniques were used to identify symptom clusters (20). However, some convergence of results was found when different statistical approaches were used to analyze data from the same sample. In a study of patients with advanced cancers (66), at the time of the initial consultation for palliative radiation therapy, symptom clusters identified using HCA and PCA correlated with each other more frequently than with the results from common factor analysis. However, symptom cluster patterns diverged at subsequent time points. In another study of patients with inoperable lung cancer (67), three symptom clusters (ie, named a pain cluster, a mood cluster, a respiratory cluster) were consistent across different methods of analysis (ie, Pearson correlation, HCA, FA).

Transferability to Other Chronic Conditions

While the assessment and analytic issues summarized above will be common to all chronic conditions, given the amount of research done to date, no evidence is available to support a generic symptom cluster that can be found across the most common chronic conditions. While instruments like the Memorial Symptom Assessment Scale have been used to assess symptoms in patients with heart failure (68–70), COPD (71,72), and HIV disease (11,73), the most valid and reliable instrument to assess symptoms for symptom cluster research across a variety of chronic conditions is yet to be developed.

Future Directions

The accurate measurement of symptom clusters is fundamental to moving this area of scientific inquiry forward. The development of a “gold standard” assessment tool necessitates that consideration be given to “breadth” vs the “depth” of symptom assessment. For example, if one wants to determine if a generic symptom cluster can be identified across a number of chronic conditions vs the identification of specific symptom cluster(s) within a chronic condition, then the choice of symptoms that need to be evaluated may be different. An equally important consideration that warrants investigation is which dimension of the symptom experience (ie, occurrence, severity, distress) should be used to create symptom clusters *de novo*. Qualitative and mixed methods studies are needed to determine the most important symptoms and the most important symptom dimensions to include on an assessment instrument that will be used to identify symptom clusters within and across chronic conditions.

In terms of the optimal analytic strategy to use to determine symptom clusters *de novo*, additional research is warranted that compares results of symptom cluster analyses across the most common statistical approaches used to date (ie, cluster analysis, factor analysis). The optimal statistical approach for

the identification of symptom clusters may vary depending on sample size, the absolute number of symptoms assessed, and the dimension of the symptom experience that is used in the analysis. Some of the opportunities identified by the panel for future research in this key area are listed in Box 1.

Targeted Interventions

State of the Science

No meta-analyses or systematic reviews were identified that focused on an evaluation of intervention studies designed for a symptom cluster. Most of the symptom management intervention studies have focused on a single symptom (eg, pain, fatigue, sleep disturbance). If the impact of a symptom-specific intervention on other symptoms was evaluated, it was a secondary aim of a study.

In a review of mind-body treatments for the pain-fatigue-sleep disturbance symptom cluster in oncology patients (74), Kwekkeboom and colleagues summarize the findings from 43 studies that used five types of mind-body interventions and demonstrated efficacy for at least two of the three symptoms. In brief, they noted that hypnosis/imagery and cognitive behavioral therapy/coping skills training interventions produced improvements in all three cancer-related symptoms individually (ie, pain, fatigue, sleep disturbance). Relaxation resulted in improvements in sleep disturbance and pain. Meditation interventions demonstrated efficacy with fatigue and sleep disturbance. Music interventions demonstrated efficacy for pain and fatigue. The authors noted that no trials were found that tested the mind-body interventions specifically for the symptom cluster of pain, fatigue, and sleep disturbance.

In a more recent review (75), Berger and colleagues noted that exercise and cognitive behavioral therapies were the most common interventions that were tested for prespecified symptom clusters in oncology patients with early- or advanced-stage disease. The authors concluded that future research needs to expand our understanding of the mechanisms that underlie multiple co-occurring symptoms. With this knowledge, mechanistically based interventions can be tested in homogenous samples of patients with specific symptom clusters.

Only one pilot study was identified that reported on the results of a randomized clinical trial (RCT) of a patient-controlled cognitive-behavioral intervention designed specifically for the symptom cluster of pain, fatigue, and sleep disturbance in oncology patients (4). Of the 86 patients with advanced lung, prostate, colorectal, or gynecologic cancers who were enrolled, 78 completed the study (ie, 36 intervention, 42 wait list control). The intervention consisted of training and use of relaxation, imagery, or distraction exercises delivered using an MP3 player for two weeks during cancer treatment. Controlling for symptom cluster severity at enrollment and other relevant covariates, symptom cluster severity at two weeks following the intervention was statistically significantly lower in the intervention group. Based on these preliminary findings, a full-scale RCT (NR013468) of this intervention is being conducted. The investigators hypothesize that the intervention will attenuate dysregulation of stress hormones and reduce the inflammatory responses that exacerbate symptoms. In addition, the intervention may decrease stress and anxiety, improve expectations for symptom outcomes, and enhance patients' perceptions of personal control.

Based on the paucity of research on the efficacy of interventions for symptom clusters other than pain, fatigue, and sleep

disturbance, a number of key questions remain unanswered. First, what is the definition of a "symptom cluster intervention"? Second, what is the scientific rationale for testing the efficacy of a symptom cluster intervention? Third, what outcome measures should be used to determine if a symptom cluster intervention is efficacious?

Transferability to Other Chronic Conditions

Given the paucity of intervention research for symptom clusters in oncology patients, no conclusions can be made about the transferability of a specific symptom cluster intervention for patients with other common chronic conditions who have the same symptom cluster.

Future Directions

Interventions that may have efficacy for symptom clusters are likely to consist of several behavioral or biobehavioral components (eg, patient education, stress management, cognitive behavioral therapy, coaching, drug treatment). Given the lack of intervention studies for symptom clusters, the optimization of a multicomponent intervention prior to the initiation of an RCT should result in a more effective, economical, efficient, and scalable intervention. One approach to achieve this goal is to use the multiphase optimization strategy (MOST) that is a comprehensive framework for the development, optimization, and evaluation of behavioral interventions, including dynamic treatment regimens (76–79). An important tool for optimization of the treatment regimen is the sequential, multiple assignment, randomized trial (SMART). A SMART is a special case of a factorial experiment. SMARTs involve multiple randomizations that are sequenced over time. Each randomization corresponds to a critical decision point and aims to address a scientific question concerning two or more treatment options at that decision point (77). While SMARTs have not been used to design interventions for symptom clusters, they have been used in intervention studies for children with autism, for children with Attention Deficit Hyperactivity Disorder, for pregnant women with drug abuse problems, and for alcohol-dependent individuals (cited in 79). Some of the opportunities for future research in this key area are listed in Box 1.

New Analytic Strategies

In the era of precision health and "big data," new analytic strategies are emerging that will undoubtedly facilitate symptom cluster research. For example, the use of machine learning may be able to identify symptom clusters *de novo* or identify patients with specific symptom clusters. The overall goal of machine learning research is to create machines (ie, computers) that can learn. One of the most common machine learning tasks is classification. In machine learning, classification algorithms induce a classifier through the use of training examples (eg, prespecified symptom cluster data). Regardless of the method of classifier training, the goal of the classifier is to determine which group a new observation should be assigned by using the information obtained in prior observations for guidance. The overall process for the creation of classifiers involves two phases. In the first phase, or the training phase, a set of data with a known outcome is used to train the classifier. In the second phase (ie, the testing phase), the performance of the classifier (eg, the identification of symptom clusters or patients

with a specific symptom cluster) is evaluated by using it to make predictions on previously unseen data (80,81).

This predictive approach to data analysis is being used in a variety of health care applications. Of particular interest is the use of machine learning techniques to analyze data from the electronic health record (80–82). If symptom data are collected on a routine basis, then machine learning techniques could be used to identify symptom clusters in patients with the most common chronic conditions. Because data in the electronic health record are collected over time, changes in the number and types of symptom clusters could be evaluated as changes in chronic conditions occur. In addition, with the availability of information from diagnostic tests (eg, lab values) and the eventual inclusion of molecular data into the electronic health record, the use of “big data analytic strategies” may allow for the identification of the molecular mechanisms that underlie the development and maintenance of symptom clusters.

Future Directions

Box 1 presents a number of recommendations that were made regarding future directions in symptom cluster research based on the evidence presented at the workshop and the discussions among the expert panel members. During these discussions, consensus was reached on all of the recommendations. While specific recommendations were made in each of the key areas that were addressed in the workshop, the panelists acknowledged considerable overlap among the questions. Clinical studies can be designed to simultaneously address multiple gaps in symptom cluster research and capitalize on the identified opportunities. Research on symptom clusters is needed across the developmental spectrum and in patients with the most common chronic conditions. Comparative studies across age groups and chronic conditions will provide insights into generic and disease-specific symptom clusters as well as the mechanisms that underlie these symptom clusters. Knowledge of molecular and behavioral mechanisms will provide vital information to design and test novel interventions for symptom clusters.

Conclusions

As stated earlier, patients rarely describe a single symptom to their clinicians. Yet evidence for how to optimally assess and manage a cluster of symptoms is lacking and represents a critical gap in symptom science. With the increasing attention to personalized care, a better understanding of individual susceptibilities to symptoms and whether a “driving” symptom triggers other symptoms within a cluster is needed. In addition, research aimed at the identification of mechanisms that underlie symptom clusters is essential to the development and testing of targeted interventions. Finally, it should be noted that the majority of the evidence reviewed and utilized by the expert panel to formulate recommendations for future directions comes from studies of oncology patients. Given the paucity of symptom cluster research, the panel members decided not to prioritize the recommendations presented in this paper; these recommendations can be used to guide research on symptom clusters in patients with cancer, other chronic conditions, and rare diseases.

Notes

The National Institute of Nursing Research thanks the Office of Rare Diseases Research, National Center for Advancing

Translational Science, and National Institutes of Health for cosponsoring this workshop.

The authors do not have any conflicts of interest to report.

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