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Symptom Clusters.

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Defining the Symptom Cluster: How Far Have We Come?

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Abstract

Objective: To examine the evolution of the concept of the symptom cluster through literature synthesis and identification of knowledge gaps.

Data source: Published literature

Conclusion: A robust body of research has developed showing that clusters of symptoms can be identified empirically with modest evidence of convergence across methods. The science would benefit from a coordinated effort of qualitative studies to ensure that appropriate symptoms are evaluated; empirical symptom cluster identification studies building upon qualitative work; and subgroup identification studies based on empirically defined symptom clusters.

Implications for Nursing Practice: Work is needed to demonstrate the value of symptom cluster identification in guiding symptom assessment and management for cancer patients and survivors.

Key words: symptom cluster, cancer, cancer-related symptoms

Following the UCSF Symptom Management Group challenge to consider the concept of the "symptom cluster" [1] and a state of the science lecture and paper on the symptom cluster in cancer [2], more recent publications have examined conceptual and methodological issues in defining symptom clusters [3-12]. For this article, a literature search of PubMed from 2008 to 2015 was conducted and reference lists of relevant publications were also scanned for additional publications. This article examines the evolution over the past 10 years of the concept of the symptom cluster including its definition, related theoretical concepts, methods of identification, stability of clusters, and identification of symptom cluster subgroups. The literature is synthesized and knowledge gaps are assessed as a basis for future research.

Definition of a Symptom Cluster

A symptom cluster has been defined as a stable group of concurrent symptoms that are related to one another and distinct from other symptom clusters [13]. Symptoms in a cluster may be related through a common etiology or mechanism, shared variance, or a common outcome [3]. Stability of clusters could relate to consistency of results across clustering techniques, consistency within cancer populations, or stability over time. To date, no firm conclusions have been drawn about the minimum number of symptoms required to form a cluster; two [1,14] or three symptoms [13] have been proposed. The dictionary defines a cluster as "a number of things of the same kind held together; a group of things" [15]. The actual number of things required is not specified; however, the use of the word "group" carries the implication that it is more than two.

However, there are arguments in favor of including symptom pairs in the definition of a symptom cluster. In two clinical studies in advanced cancer patients, a gastro-intestinal symptom cluster was determined to be made up of two symptoms, nausea and vomiting [16,17]. In a large sample of advanced cancer patients, anxiety-depression was identified as a cluster across three different methods of analysis [18,19]. Given the presence of clinically and statistically meaningful symptom pairs and the potential for others, it makes sense to include symptom pairs in the definition of a symptom cluster. Another reason to consider symptom pairs as clusters is that the number and type of symptoms observed in a cluster is

reflective of the number and type of symptoms that were measured. Measuring a larger number of related symptoms is likely to increase the number of symptoms included in a particular cluster. When fewer symptoms are measured, a symptom pair could be a proxy for a cluster with more symptoms. Including symptom pairs in the definition of a cluster provides an opportunity for a more complete description of symptom clusters in a specific context.

On the other side of this issue are questions about when a symptom cluster should be considered complete. As noted above, one determinant of the number of symptoms comprising a cluster is the number and relevance of the symptoms that are measured. Other determinants include characteristics of specific cancers (such as, cough and breathlessness associated with lung cancer) [20,21], treatment modalities (neuropathy related to neurotoxic chemotherapy), and demographics (a body image cluster in women with gynecological cancers) [22]. Acknowledging these influences, experts have begun to advocate for agreement about a core set of symptoms to be measured across all patients[23,24] as well as consideration of symptom clusters specific to disease [25,26] and treatment types [27]. This issue is described more fully in the paper on assessment of multiple co-occurring symptoms ([28]).

Related Theoretical Concepts

Across symptom management theories and models, the addition of the concepts of interaction [29], time [30], and mechanism [31] have proven to be important constructs guiding our scientific understanding of the symptom cluster. As the science of symptom management has developed, the theories and models used to describe symptom clusters have expanded to incorporate explicit components. The Theory of Symptom Management, proposed three components originally: the symptoms experience (addressing single or multiple symptoms); symptom management; and outcomes [1]. Later, this theory was expanded to include personal, health-illness, and environmental contexts of symptoms [32]. The Theory of Unpleasant Symptoms explicitly described the potential for interaction and/or synergy among multiple symptoms [29]. Through a linear presentation of antecedents, symptoms, and outcomes, it suggested but did not explicitly identify a time component. Later theoretical models expanded the time component, recognizing that symptoms can vary considerably over time and that variability in one symptom can influence other

symptoms [33,34]. One model, The Symptom Interaction Framework, explicitly identified underlying symptom "mechanisms" to describe alterations in process or function that could explain the presence of a group of symptoms [31]; mechanisms could be biological, psychological, social, or behavioral.

Methods of Identification of Symptom Clusters

Qualitative methods allow for the exploration of the breadth and complexity of related symptoms. Four qualitative studies identified symptom clusters (table 1)[20-22,35]. Women with gynecological cancers identified the symptoms of tiredness, sleeplessness, pain, depression, and weakness as the most common cluster experienced by all participants over one year, irrespective of treatment [22]. Three other symptom clusters were identified in this research, all related to chemotherapy (body image, GI and neuropathy). In a longitudinal qualitative study of symptoms related to lung cancer, a subset of respiratory symptoms including cough, breathlessness, and fatigue were highlighted as co-occurring, influencing one another, and triggering other symptoms such as anxiety, depression, pain, and sleep disturbance [21]. The investigators did not discuss why the triggered symptoms were not part of the cluster. In another lung cancer sample, the core symptoms of fatigue, pain, cough, and breathlessness were associated and affected one another synergistically [20]. However, the investigators noted that participants often focused on individual symptoms and not all symptoms were given equal weight. In a study of chemotherapy-induced nausea, the investigators explored the possibility that the term nausea could represent a cluster of symptoms[35]. They concluded that the nausea experience included a cluster of symptoms that was unique to each individual. Although the research identified a group of co-occurring symptoms that were considered separate but related to nausea (vomiting, taste changes, appetite changes, and fatigue), the investigators did not identify this as a symptom cluster. More rigorous qualitative research is needed to ensure that symptom clusters identified through patient narrative support or challenge the current definition of a symptom cluster.

***A priori* Identification**

In oncology symptom research, symptom clusters have been identified using two different methods: 1) they have been specified "*a priori*", meaning formed or conceived beforehand; or 2) they

have been identified using empirically, based on observation (also called "de novo") methods [3]. *A priori* refers to symptoms selected as a cluster based on patient qualitative experience, clinical observation of symptom co-occurrence, or research hypotheses about the relationships among symptoms. Symptom clusters identified in qualitative studies could be considered *a priori* if the individuals being studied determine the symptom selection; alternatively, they could be considered empirical if the clusters are derived through qualitative data analysis.

Quantitative research has been used to study *a priori* symptom clusters. In animal studies, a group of behaviors (asthenia, lethargy, anorexia, weakness, and sleep disturbance) were observed that became known as "sickness behavior," a syndrome thought to be the result of inflammatory processes induced by disease or trauma[36,37]. This syndrome closely resembles the cluster of symptoms commonly reported by humans in the context of cancer and its treatment that may include fatigue, sleep disturbance, pain, depression, and mental confusion. The similarities between human symptoms and animal behaviors resulted in many investigations in which variations on this group of symptoms were evaluated as *a priori* symptom clusters [30,38-43].

A priori symptom clusters have included variations on the symptoms of fatigue, insomnia, pain, and depressed mood that are related to sickness behaviors (table 2)[30,38-44]. Quantitative studies have demonstrated that these clusters meet two criteria defining a cluster: symptoms are related to one another and have a common influence on outcomes. Most studies used analytic techniques such as correlation, path analysis, structural equation modeling, or other multivariate methods to examine the relationships among a group of symptoms. One study showed that fatigue, sleep disturbance, and depression in breast cancer patients were correlated at each study point; and path analysis showed that symptom severity at each time point predicted severity of the same symptom at subsequent time points with the exception that earlier fatigue predicted later depression in pre-menopausal women[38]. Another study examined temporal changes in daily symptoms (fatigue sleep disturbance, and depressed mood) selected *a priori* in women with gynecological cancers and found that greater sleep disturbance was associated earlier peak fatigue, and higher levels of fatigue predicted later depressed mood[30]. Another study modeled fatigue as a latent

variable directly influenced by pain, depressed mood and insomnia[43]. Results showed direct effects among all four symptoms as well as mediating effects: the effect of depressed mood on pain was mediated by insomnia; and the effect of depressed mood on fatigue was mediated by insomnia and pain.

The effect of a presumed symptom cluster on outcomes has also been examined. For example, multiple regression analysis showed that the cluster of pain, fatigue, insomnia, and mood disturbance predicted performance status and quality of life in elderly cancer patients[39]. In another study, pain, the cluster of fatigue, sleep disturbance, and distress in lung cancer surgery patients was negatively related to performance status and quality of life[41]. Only one study examined how related symptoms influenced outcomes. In a cross-sectional study of fatigue, insomnia, depression, and pain, a cluster was defined as two or more symptoms directly related to each other and indirectly related to functional performance (dependent variable)[44]. Path analysis revealed seven indirect symptom paths to functional performance for pain and three paths for insomnia which the investigators characterized as synergy among symptoms.

Empirical Identification

The selection of an *a priori* symptom cluster does not settle the issue of the completeness of a cluster or the number of symptoms that are or should be included. It is possible that other symptoms could be part of the cluster but were left out because of *a priori* selection of symptoms. To address the completeness issue, an alternative approach has been to use statistical procedures to select and group symptoms from a larger population of symptoms. Thus, an empirically determined symptom cluster is a group of symptoms derived from a larger pool of symptoms using statistical procedures (table 3)[7,16,45-58]. In this methodology, research participants rate a group of symptoms that are relevant to their situation. A variety of statistical methods such as principal components analysis, common factor analysis, or cluster analysis are used to select clusters from the larger pool of symptoms.

Principal Components Analysis (PCA), a type of exploratory factor analysis, is a descriptive data reduction method based on total variance [59] that combines a larger number of variables into smaller clusters that are unique and stable. This method does not presume a theoretical basis or underlying connection among the symptoms within each cluster. PCA has been the method most commonly used

for symptom clustering [16,19,54,58,60]. For example two studies of advanced cancer patients used PCA to identify symptom clusters using the Edmonton Symptom Assessment Scale (ESAS). The first study identified two clusters: cluster 1 included fatigue, drowsiness, nausea, appetite, and dyspnea; cluster 2 comprised anxiety and depression [46,47]. The second study used the ESAS measure, but supplemented it with 13 additional items [16], identifying four clusters: confusion, neuropsychological, anorexia-cachexia, and gastro-intestinal clusters. In both studies, symptom clusters differed by age, gender, performance status, and/or type of cancer. The difference between the study results could also be related to the symptoms measured. A third study used PCA to identify three clusters in breast cancer patients based on a 32-item symptom scale: emotional, unwell, and gastro-intestinal clusters [50]. The first cluster included similar symptoms to the

Common Factor analysis (CFA) is another type of exploratory factor analysis that examines common variance to determine the latent factors underlying a set of variables and develop and/or test hypotheses about those underlying factors [59]. Two symptom cluster studies using CFA illustrate this point. In a study of breast and prostate cancer patients being treated with radiotherapy, CFA was used to identify symptom clusters in 160 individuals who rated 32 symptoms on the Memorial Symptom Assessment Scale [51]. At the midpoint of treatment, three clusters were identified: a mood-cognitive cluster (difficulty concentrating, feeling nervous, feeling sad, worrying, itching, feeling irritable, skin changes); a sickness behavior cluster (pain, lack of energy, feeling drowsy, difficulty sleeping, sweats); and a treatment-related cluster (urinary problems and diarrhea). In a separate study, 282 women receiving chemotherapy or radiotherapy for breast cancer rated twenty symptoms [52]. Two symptom clusters were identified during treatment: a psycho-neurological cluster (pain, fatigue, insomnia, depressed mood, cognitive disturbance, and hot flashes); and an upper gastro-intestinal cluster (nausea, vomiting, decreased appetite). The "sickness behavior cluster" in the breast and prostate study was similar to the "psycho-neurological cluster in the breast cancer study.

Two things are noteworthy. First, the results provided empirical validation of the "sickness behavior" cluster that was previously identified *a priori*. Secondly, implicit in the naming of the clusters

was a hypothesis about the underlying mechanism. The "sickness behavior" cluster and the "psycho-neurological" cluster both have a hypothesized underlying mechanism of inflammation. Although the symptoms included in each cluster are slightly different, some of the core symptoms are the same, lending modest support to the idea that there is a common mechanism underlying this group of symptoms.

Hierarchical Cluster analysis (HCA) is an empirical method for grouping symptoms or people and separating them from dissimilar groups based on measures of distance, such as Euclidian distance [61]. In a study of 922 advanced cancer patients in a palliative medicine program, HCA was used to group 25 symptoms [53]. Seven clusters were identified: fatigue-anorexia-cachexia, psycho-neurological, upper gastro-intestinal, nausea-vomiting, aero-digestive, debility, and pain clusters. The authors argued that these clusters were likely to be therapeutically important because treatment of one symptom could influence or be influenced by another symptom in the cluster. For example, the pain cluster included both pain and constipation; in advanced cancer, pain is a common problem that is often treated with opioid analgesics that can induce constipation.

Stability of Symptom Clusters

Consistency across Clustering Techniques. In a number of studies, investigators have searched for symptom clusters using more than one analytic technique (table 4)[19,60,62-67]. Looking across clustering methods, one can observe both similarities and differences in the number and composition of symptom clusters. A study of 1296 advanced cancer patients illustrated this point [62]. The cluster of anxiety and depression was identified across all three clustering methods (PCA, HCA, and CFA). Two identical clusters also emerged when analyzed with PCA and HCA: one cluster included appetite, nausea, wellbeing, and pain; the other included fatigue, drowsiness, and dyspnea. With CFA, only one additional factor emerged combining all the remaining symptoms into one factor. The investigators concluded that PCA and HCA were in closer agreement than CFA. Another example of agreement between PCA and HCA can be seen in a study of 400 patients with inoperable lung cancer [60]. Three symptom clusters (pain, mood, and respiratory) were consistent across three different methods of analysis: Pearson correlation,

PCA, and HCA. Looking across studies, appetite change, proposed in qualitative research as an additional component of a nausea-vomiting cluster [35], was confirmed in two empirical analyses [52,56].

Consistency within Cancer Populations. Looking at similar cancer populations, several review papers concluded that there is little consistency of symptom clusters across samples. For example, a review of five breast cancer studies found no cluster consistency across studies [10]. A review of gastrointestinal symptom clusters [11] found that 38 of 40 clusters included different symptoms; and a review of five lung cancer studies showed only nausea/vomiting and a respiratory cluster were common across two studies [9]. In a review of studies of patients with advanced disease, the authors could not formulate a general consensus of symptom clusters due to variability in symptoms assessed, assessment measures used, analytic methods, and patient demographics [12].

Stability over Time

Over the past decade, evidence has accumulated in support of the stability of symptom clusters over time. Symptoms evaluated with exploratory factor analysis at the middle, end, and 1 month after radiotherapy for breast or prostate cancer showed four relatively similar symptom clusters across time points: mood-cognitive; treatment-related; sickness-behavior; and pain [51]. For breast cancer patients undergoing treatment, a psycho-neurological symptom cluster was observed via common factor analysis prior to treatment; this cluster was repeated during treatment and a gastro-intestinal cluster was also observed [52]. Symptom clusters identified before treatment in women with ovarian cancer were repeated during chemotherapy; additional clusters were observed during treatment that could represent the short- and long-term effects of treatment [49]. These studies and many others provide increasing support for the clustering of symptoms by virtue of their concurrence and stability over time.

Antecedents and Consequences

A better understanding of the antecedents and consequences of a symptom cluster could inform our understanding of who is likely to experience specific clusters and how the clusters influence their quality of life. Cluster composition has been shown to differ by age and gender [47] and by performance status and cancer diagnosis[16] in two different studies. In contrast, another study found no differences in

symptom cluster composition based on demographic or clinical factors [52]. With regard to consequences of symptom clusters, the number of symptom clusters experienced [16] and the presence of a specific symptom cluster [67] were associated with survival/mortality. In addition, more symptoms [41], more severe symptoms [66], and the presence of specific clusters [56] have predicted poorer quality of life. More work is needed to point us toward a more robust picture of the demographic and clinical context of specific symptom clusters as well as the likelihood that specific clusters influence important outcomes including quality of life and survival.

Identification of Patient Subgroups with a Similar Symptom Experience

Thus far, we have examined the way in which "symptoms" are related to one another. An alternative approach is to examine differences in the symptoms experience within "subgroups" of individuals (table 5)[68-77]. Regardless of how a symptom cluster has been determined (*a priori* or empirically), there is likely to be variability in how individuals experience the cluster. One method of grouping patients is to create composite symptom scores. Sanford and colleagues [76] selected fatigue, sleep disturbance, depression, anxiety, and confusion as an *a priori* cluster in women undergoing chemotherapy for breast cancer. Participants were assigned to a symptom cluster index group based on the number of abnormal symptom scores at the initial assessment. With the exception of anxiety, the coherence and stability of each symptom cluster group was demonstrated by similar patterns of symptom severity and change over time in all four symptoms. Using a similar methodology to classify groups of breast cancer patients on the basis of fatigue, sleep disturbance, and depression, Liu et al [74] found a similar pattern of symptom cluster groups across time.

Statistical grouping methods have also been used to evaluate groups of individuals to determine the prevalence and pattern of symptoms within cluster groups. Hierarchical Cluster analysis (HCA), previously described as a method for grouping symptoms, has also been used to identify subgroups of individuals with similar symptom patterns; Latent Class Analysis (LCA) has also been used for this purpose. Based on HCA of the most common symptoms (fatigue, pain, dyspnea, and insomnia), lung cancer patients were classified into groups with mild (60%), moderate (28%) or severe (12%) composite

symptom scores [70]. Another study used HCA to evaluate severity patterns of the psycho-neurological symptom cluster (including fatigue, insomnia, pain, depressed mood, and cognitive disturbance) in breast cancer patients to identify four groups: all low symptoms (26%), all high symptoms (24%), low pain-high fatigue (19%), and high pain (30%) groups [73]. In a separate study, breast cancer patients were classified using LCA into subgroups based on symptoms (fatigue, insomnia, pain, and depression); subgroups included all low symptoms (61%), all high symptoms (7%), and low pain-high fatigue (32%) [69]. Despite some variation in results, these studies indicate that groups of cancer patients can be classified according to similarities in their experience of symptom clusters.

Stability of Symptom Cluster Subgroups over Time

There is some evidence that symptom cluster subgroups endure over time. Prior to radiotherapy, men with prostate cancer were classified into four subgroups with similar patterns of fatigue, insomnia, pain, depressed mood, anxiety, and treatment-related symptoms (bowel, urinary, and sexual): all low symptoms; moderate treatment-related symptoms; all high symptoms; and moderately high fatigue, depression, and anxiety with few treatment-related symptoms [68]. Similar groupings were derived after treatment. In breast cancer patients undergoing treatment, before treatment subgroups were replicated during treatment and two new groups emerged: high depressed mood-cognitive disturbance and high fatigue-insomnia groups [73].

Antecedents and Consequences of Symptom Cluster Subgroups

Symptom cluster subgroups were shown in one study to differ by treatment received, performance status, and education [73]; however, another study observed no differences based on demographic or clinical factors [74]. Considering biomarkers, several investigators were able to differentiate subgroups based on the presence of rare cytokine gene alleles [69], the additive effects of five immune response genes [75], or cytokine levels [77]. With regard to outcomes, research has shown that subgroups with more severe symptom clusters had poorer quality of life [70,71], worse functional status [73], and increased depression and worse mental quality of life [66]. Continued work in this domain will benefit the identification of subgroups at high risk for potentially damaging effects on patient outcomes.

Synthesis and Conclusions

Advances in Defining the Symptom Cluster

There have been significant advances in symptom cluster science over the past decade. With regard to the definition of a symptom cluster, examples in the literature of clinically meaningful symptom pairs such as nausea-vomiting [16,17] or anxiety-depression [18] add strength to the argument for including symptom pairs within the definition of the symptom cluster. More is to be gained than lost in accepting the more inclusive definition. In addition, several theoretical concepts have been incorporated into symptom models to guide the study of symptom clusters including evaluation of influences of symptoms on one another, examination of cluster stability over time, and determination of underlying mechanisms. An evidence base is developing to support the relevance of these concepts to the science of symptom clusters.

Advances in Research and Future Directions

It is interesting to note that cancer patients and survivors have been able to recognize and articulate groups of inter-related symptoms that impacted their quality of life. Symptom cluster science could benefit from more focused qualitative explorations of symptom clusters across the cancer trajectory from diagnosis, through treatment, and into survivorship. Learning from patients and survivors which symptoms co-occur reliably, are most distressing, and/or result in the most interference with functional status and quality of life will better inform quantitative science by ensuring that all relevant symptoms are represented in models. This will also enhance the validity of the quantitative models as representations of the patient-survivor experience. It may also be useful to use qualitative research to validate statistically derived symptom clusters as congruent with patient symptoms experience.

There is now a robust body of research showing that clusters of symptoms can be identified empirically using a variety of statistical methods. There is modest evidence of convergence across empirical clustering methods applied within the same sample. However, there is less evidence of convergence and validation of clusters across similar samples using the same or different analytic strategy. Therefore, replication studies are needed to ensure the reproducibility and usefulness of the

statistically identifiedsymptom cluster in the clinical setting. Looking across methods used in symptom cluster research to date, the science would benefit from a coordinated effort of qualitative studies to ensure that appropriate symptoms are evaluated for clustering; empirical symptom cluster identification studies that build upon that qualitative work; and studies identifying patient subgroups based on empirically defined symptom clusters. This progression would enhance the validity and reproducibility of symptom cluster research.

Scientists have explored demographic, personal, and clinical characteristics associated with symptom clusters and cluster subgroups. There is also research evidence that symptom clusters influence clinical outcomes including quality of life and survival. This information is important for the identification of symptom cluster phenotypes—that is, subgroups with similar symptom patterns, identifying characteristics, and probable outcomes. Continuing work is needed to identify high risk groups (at risk for more severe symptoms and/or worse outcomes) that can be targeted for intervention development and evaluation. Ultimately there is a need to demonstrate the value of symptom cluster identification in guiding symptom assessment and management for cancer patients and survivors.

Table 1. Identification of Symptom Clusters in Qualitative Research

Authors	Sample	Design	Method	Symptom Clusters	Covariates/Outcomes
Lopez, et al. [22]	10 women in U.K. with GYN cancers	Longitudinal: Pre-treatment to 12 months post-treatment 39 interviews	Content Analysis	1. Tiredness, sleeplessness, pain, depression, weakness 2. Hair loss, ocular changes, body image, identity experience, anxiety 3. Nausea, appetite loss, taste changes, bowel function, weight changes, distress 4. Numbness-tingling in hands and feet, restlessness, sleeplessness, depression	Physical symptoms interrelated with depression, uncertainty, body image, and identity as cancer patient.
Maguire, et al. [20]	10 individuals in U.K. with advanced lung cancer reporting 3+ symptoms	Longitudinal: 2 interviews 3-5 weeks apart	Interpretative Phenomenological Analysis (IPA)	1. Cough, pain, insomnia 2. Breathlessness, appetite loss, weight loss 3. Fatigue, nocturia, disrupted sleep	Detrimental impact on physical functioning
Molassiotis, et al.[21]	17 individuals in U.K. with inoperable lung cancer	Longitudinal: Beginning of treatment, 3, 6, 12 months	IPA	1. Cough, breathlessness, fatigue, sleep disturbance, anxiety	• Cough associated with sleeplessness; • Sleeplessness triggered fatigue; • Coughing worsened breathlessness; • Breathlessness triggered anxiety
Olver, et al. [35]	42 cancer patients in Australia with chemotherapy-induced nausea	Cross-sectional	Thematic analysis	Separate concomitant symptoms experienced with nausea: vomiting, appetite changes, taste changes, fatigue	

Table 2. *A Priori* Identification of Symptom Clusters in Quantitative Research

Authors	Sample	Design	Method	Symptom Clusters	Covariates/Patterns/Outcomes
Cheng, et al.[39]	120 elderly Chinese cancer patients undergoing treatment	Cross-sectional Symptom Distress Scale (SDS); 4 symptoms selected for analysis	Multiple Regression Independent variables: symptoms Dependent variables: functional status, quality of life	Symptom cluster: pain, fatigue, insomnia, mood disturbance	• 20% of sample reported any 2 symptoms; 29%; reported any 3 symptoms; 33% reported all 4 symptoms • Low to moderate correlations between symptom pairs • All 4 symptoms had independent effects on quality of life
Ho, et al. [38]	137 breast cancer patients in U.S. treated with chemotherapy	Longitudinal: Pre-, post, and 6-8 months Validated symptom scales	Path Analysis	Symptom cluster: Fatigue, sleep disturbance, depression	• All symptoms were correlated at each time point; • Prior symptom severity predicted subsequent severity of same symptom. • In pre-menopausal women, baseline fatigue predicted post-treatment depression; and post-treatment fatigue predicted depression at final follow-up.
Hoffman, et al.[40]	80 newly diagnosed lung cancer patients in U.S. undergoing chemotherapy	Cross-sectional Baseline observation Cancer Symptom Experience Inventory; 3 symptoms selected for analysis	Multinomial log-linear modeling	Symptom cluster: pain, fatigue, insomnia	• 3-way interaction among symptoms • Covariates of age, comorbidities, and stage of disease did not improve the model
Jim, et al. [30]	78 U.S. women with GYN cancers being treated with chemotherapy	Longitudinal: Daily symptom ratings for 7 days; actigraph for 7 days	Latent Change Scores	Symptom cluster: Fatigue, sleep disturbance, depressed mood	Symptoms occurred in cascade pattern: • Higher level of sleep disturbance was associated with earlier peak of fatigue • Higher fatigue level was associated with higher subsequent

					depressed mood.
Lin, et al. [41]	145 Chinese lung cancer patients post-surgery	Cross-sectional One week post-surgery MD Anderson Symptom Inventory (MDASI); 4 symptoms selected based on prevalence and severity	Multiple regression Independent variables: symptoms Dependent variable: quality of life	Symptom cluster: fatigue, pain, sleep disturbance, distress	• Presence of more symptoms associated with poorer quality of life • In hierarchical regression, fatigue, sleep, and distress accounted for 72% of variance in quality of life
Oh, et al. [44]	110 South Korean cancer patients undergoing treatment	Cross-sectional Validated symptom scales	Path Analysis Symptom cluster defined as two or more symptoms directly related to each other and indirectly related to outcome Dependent variable: functional performance	Symptom cluster: pain, insomnia, depression, fatigue	• 7 indirect paths between pain and functional performance (pain-insomnia, pain-depression, pain-fatigue, pain-depression-fatigue, pain-insomnia-depression-fatigue) • 3 indirect paths between insomnia and functioning (insomnia-depression, insomnia-fatigue, insomnia-depression-fatigue)
So, et al. [42]	215 Chinese women undergoing treatment for breast cancer in Hong Kong	Cross-sectional During treatment Validated symptom scales	Correlation; Structural Equation Modeling (SEM)	Symptom cluster: Fatigue, pain, anxiety, depression	• Correlation among symptoms supported existence of symptom cluster • More severe symptoms, treatment with chemotherapy, and lower social support was associated with poorer quality of life
Stepanski, et al.[43]	11,445 U.S. cancer patients undergoing treatment	Cross-sectional During treatment Patient Care	SEM: Test sample and validation sample	Symptom cluster: Fatigue, trouble sleeping, depressed mood, pain	Direct effects: • Fatigue, modeled as a latent variable, was influenced by depressed mood, trouble sleeping, and pain.

		Monitor • Validated scale with 86 symptoms • 4 symptoms included in analysis			Indirect effects: • effect of depressed mood on pain mediated by trouble sleeping • effect of trouble sleeping on fatigue mediated by pain; • effect of depressed mood on fatigue mediated by trouble sleeping and pain. Cross-validation of model was supported by validation sample

Table 3. Empirical Identification of Symptom Clusters

Authors	Sample	Design	Method	Description of Clusters	Covariates/Patterns/Outcomes
Brown, et al. [45]	196 U.S. women 6 months to 5 years post-diagnosis of Non-small cell lung cancer	Cross-sectional Lung Cancer Symptom Scale (LCS)	Novel strategy for identification of symptom clusters using dummy codes	1. 3-symptom cluster: no pattern of symptoms across participants 2. 4-symptom cluster: fatigue, shortness of breath, cough, anorexia 3. 5-symptom cluster: fatigue shortness of breath, cough, pain, anorexia (reported by 64% of sample) 4. 6-symptom cluster: 5-symptom cluster plus hemoptysis	• Depressed mood, time since diagnosis, number of comorbidities, and current treatment status were related to overall symptom severity
Cheung, et al.[46] Cheung, et al.[47]	1,366 Canadian patients with advanced cancer attending palliative care clinics	Cross-sectional Edmonton Symptom Assessment Scale (ESAS)	Principal Components Analysis (PCA)	1. Fatigue, drowsiness, nausea, appetite, dyspnea 2. Anxiety, depression	• Clusters 1 and 2 accounted for 45% and 10% of total variance, respectively; • Clusters differed by primary cancer site although cluster 2 was consistent across sites • Clusters differed by age and and gender: fatigue and drowsiness were included in cluster 1 for younger but not older patients; in men, pain was part of cluster 2; for women, physical and psychological symptoms formed separate clusters
Gleason, et al. [48]	66 U.S. patients newly diagnosed with brain tumors being treated with radiotherapy	Longitudinal Pre-treatment, end of treatment FACT-Brain CESD-Depression	Exploratory Factor Analysis (EFA)	1. Language: difficulty reading, writing, finding works 2. Mood: sadness, anxiety, depressed mood	• A 3rd factor included only one symptom, so it was dropped • Factor structure at end of treatment was consistent with pre-treatment • Multidimensional scaling and cluster analysis supported 2-factor structure

Huang, et al. [49]	111 Chinese ovarian cancer patients undergoing chemotherapy	Longitudinal Pre-, during chemotherapy MSAS	PCA	Pre-treatment 1. Pain-related: Pain, bloating, dizziness 2. Psychological: Nervous, sad, anxious 3. Menopausal: Lack of energy, dry mouth, difficulty sleeping, sweats, lack of appetite, irritation Cycle 1 4. Gastro-intestinal: Nausea, vomiting, weight loss 5. Body image: Hair loss, constipation Cycle 3 6. Neurological: Numbness-tingling, dizziness	• Clusters 1, 2, and 3 were stable across time points • The addition of new symptom clusters may be attributed to short- and long-term effects of treatment.
Jimenez, et al. [16]	406 Spanish patients with advanced cancer enrolled in a palliative care program	Cross-sectional ESAS; 13 single symptoms	PCA	1. Confusion cluster: agitation, confusion, urinary incontinence 2. Neuropsychological cluster: Anxiety, depression, insomnia 3. Anorexia-cachexia cluster: Anorexia, weight loss, tiredness 4. GI cluster: Nausea, vomiting	• Symptom clusters differed by cancer site, gender, age, and performance status • Survival was related to the number of symptom clusters present
Kenne Sarenmalm, et al.[50]	206 Swedish breast cancer patients undergoing treatment	Longitudinal Diagnosis, weeks 1 and 3, 6 months MSAS	PCA	1. Emotional: sad, nervous, worry, difficulty sleeping, quality of life 2. Unwell: drowsy, dry mouth, appetite loss, irritability, difficulty swallowing, shortness of breath 3. GI: weight loss, taste change, constipation, vomiting, hair loss, nausea	• PCA Clusters 1 and 3 were consistent across all time points; cluster 2 was less consistent
Kim, et al. [51]	160 U.S. breast or prostate cancer patients being	Longitudinal Pre-treatment,	EFA	Factor structure at middle of radiotherapy: 1. Mood-cognitive:	• Symptom clusters identified at end of treatment and one month later were not identical to mid-

	treated with radiotherapy	middle and end of treatment, 1 month later MSAS		concentration, feeling nervous, sadness, worry, itching, irritability, skin changes 2. Sickness behavior: pain, lack of energy, drowsiness, sleep difficulty, sweating 3. Treatment-related: urinary problems, diarrhea	treatment clusters; however, the mood-cognitive and sickness behavior clusters were very similar.
Kim, et al. [52]	282 U.S. breast cancer patients treated with chemotherapy or radiotherapy	Longitudinal Pre-treatment, during treatment, end of treatment 20 symptoms (some single items, some validated scales)	Common Factor Analysis (CFA)	Pre-treatment 1. Psycho-neurological: Depressed mood, cognitive disturbance, fatigue insomnia, pain First follow-up 1. Psycho-neurological (hot flashes added) 2. Gastro-intestinal: nausea, vomiting, low appetite Second follow-up 1. Psycho-neurological 2. Gastro-intestinal	• Clustering of symptoms was consistent across treatment trajectory • Demographic and clinical variables did not influence clustering
Kirkova, et al. [7] Walsh, et al. [53]	922 U.S. patients with advanced cancer in palliative care program Validation sample of 181 patients	Cross-sectional 25 symptoms with prevalence > 15%	Hierarchical Cluster Analysis (HCA)	1. Fatigue-anorexia-cachexia cluster: fatigue, lack of energy, weakness, dry mouth, anorexia, early satiety, taste change, weight loss 2. Neuro-psychological cluster: sleep problems, anxiety, depression 3. Upper GI cluster: dizzy spells, dyspepsia, belching, bloating 4. Nausea-vomiting cluster: nausea, vomiting 5. Aero-digestive cluster: dyspnea, cough, hoarseness, dysphagia 6. Debility cluster: edema, confusion 7. Pain cluster: pain, constipation	• Kirkova: Validation study clusters were similar but not identical (8 clusters)

Molassiotis, et al.[54]	143 patients in U. K. cancer centers	Longitudinal Pre-treatment, 3, 6, 12 months later MSAS	PCA	Pre-treatment: 1. Nausea, vomiting, bloating 2. Numbness-tingling hands, feet; swelling arms-legs 3. Hair loss; do not like self 4. Shortness of breath, cough 5. Difficulty swallowing, weight loss, low appetite, vomiting, pain 6. Feeling sad, worrying, nervous, difficulty concentrating, dizziness, drowsiness, Irritability, lack of energy	At subsequent time points, PCA used again to determine core symptoms: • At 3- and 6-month assessments, core symptoms were maintained but new symptoms entered some clusters • At 12 months, clusters decreased in number of items Overall, the six clusters remained relatively consistent over time
Olson, et al. [55]	82 patients in Canada receiving palliative care	Longitudinal 1 month and 1 week before death ESAS	SEM Exogenous (background) variables: pain, anxiety, nausea, shortness of breath, drowsiness Endogenous (dependent): appetite, tiredness, depression, wellbeing	Stable effects across time periods: • Drowsiness predicted appetite • Drowsiness predicted tiredness • Anxiety predicted depression	Conclusion: There were different and changing causal structures underlying connections between symptoms
Pirri, et al. [56]	200 newly diagnosed Australian cancer patients undergoing combined modality treatment	Longitudinal Pre-, on-, post-treatment EORTC QLQ-C30 Selby quality of life scale	PCA used to identify any symptom cluster that included nausea and vomiting	• 6-factor solution • Gastro-intestinal (GI) cluster (nausea, vomiting, appetite loss) at every time point	• Controlling for covariates, GI cluster predicted overall quality of life impairment at end of treatment • The moderating effects of all 3 symptoms on quality of life was stronger than any single symptom or symptom pair
Skerman, et al.[57]	219 Australian cancer patients	Longitudinal	CFA	Over time, 5 consistent symptom clusters were characterized:	• Several symptoms were associated with different clusters

	being treated with chemotherapy	Within 1 month of initiating chemotherapy, 6, 12 months later Rotterdam Symptom Checklist—42 symptoms		1. Vasomotor: sweating, hot/cold spells, night sweats 2. Oral discomforts: difficulty swallowing, sore throat, sore mouth, pain swallowing 3. Upper gastro-intestinal/aero-digestive discomforts: indigestion, heartburn, belching 4. Gastro-intestinal toxicities: poor appetite, vomiting, nausea, shivering, stomach pain, trembling 5. Musculoskeletal discomforts, lethargy: fatigue, sleepiness, muscle soreness, weakness	over time: poor appetite, weakness, and fatigue • Vasomotor, oral, and musculoskeletal clusters were replicated over time, retaining over 75% of the original symptoms
Tsai, et al. [58]	427 Taiwanese patients with advanced cancer admitted to a palliative care unit	Cross-sectional Upon admission Face-valid symptom reporting scale—15 items	PCA	1. Loss of energy: fatigue, weakness 2. Poor intake: anorexia, taste changes, dysphagia, constipation, dry mouth 3. Autonomic dysfunction: restlessness, heat, dizziness, insomnia, night sweats 4. Aero-digestive impairment: nausea, vomiting, abdominal fullness, dyspnea 5. Pain	

Table 4. Comparison of Methods for Identification of Symptom Clusters

Authors	Sample	Design	Method	Clusters or Subgroups	Covariates/Outcomes
Chen, E. [18] Fan, G. [19]	1296 Canadian patients with advanced cancer referred to outpatient palliative care service	Longitudinal Baseline, 1-, 2-, 4-, 8-, and 12-weeks ESAS	PCA, HCA, EFA	Baseline: PCA 1. Appetite, nausea, wellbeing, pain 2. Fatigue, drowsiness, dyspnea 3. Anxiety, depression EFA: 1. Fatigue, drowsiness, dyspnea wellbeing, appetite, pain, nausea, 2. Anxiety, depression HCA re-dividing cluster 1: 1. Fatigue, drowsiness, dyspnea 2. Appetite, nausea, wellbeing, pain 3. Anxiety, depression	• The number and composition of symptom clusters varied over time • Using the same analysis method, clusters were consistent over time • Symptom pairs (anxiety and depression; fatigue and drowsiness) were consistently in the same cluster with shifting of other symptoms over time • Results for PCA and HCA were more consistent across methods than EFA
Cheville, A.[63,64]	2405 U.S. lung cancer survivors up to 5 years post-diagnosis	Longitudinal: 1, 2, 3, 4, 5 years LCS; single items: sleep quality; emotion, social, cognitive wellbeing	HCA, EFA, Latent Trait Analysis (LTA)	HCA: 1-5 years 1. Dyspnea, cough, fatigue EFA 1. Dyspnea, cough, fatigue LTA: 1. Fatigue, dyspnea, cough 2. Emotional wellbeing, sleep	• A single symptom cluster was consistent across analytic methods • Presence of the symptom cluster, each component symptom, and symptom pairs were associated with decreased survival • Differences were small between the capacity of symptom clusters, pairs or individual symptoms to predict survival
Henoch, I. [60]	400 Swedish newly diagnosed Swedish lung cancer patients	Cross-sectional 1 month post-diagnosis SDS, EORTC QLQ-C30 (the same 11 items from each	Correlation, PCA, HCA	Correlation: EORTC and SDS 1. Pain cluster: pain, bowel, nausea, appetite, fatigue 2. Mood cluster: insomnia, mood, concentration, outlook 3. Respiratory cluster (SDS only): dyspnea, cough	• Clusters were judged to be consistent across measures and analytic methods

		scale)		PCA: EORTC and SDS 1. Pain cluster 2. Mood cluster 3. Respiratory cluster HCA: EORTC and SDS 1. Mood cluster 2. Respiratory cluster 3. Pain cluster: pain, bowel, nausea 4. Appetite, fatigue: closely related to each other and to pain cluster	
Maliski, S. [65]	402 U.S. men with prostate cancer undergoing treatment	Cross-sectional 8-12 months post-treatment PCI-SF: urinary, sexual, bowel dysfunction; SF-36: fatigue, pain, emotional distress	FA, HCA	FA: 1. Fatigue, emotional distress 2. Sexual and bowel dysfunction; pain [urinary dysfunction loaded equally on both factors] HCA: Subgroups 1. Most pain, some fatigue, some sexual dysfunction (10%) 2. Most urinary and sexual dysfunction (19%) 3. Most fatigue, most emotional distress, some sexual dysfunction (14%) 4. Most bowel dysfunction, some sexual dysfunction (10%) 5. Minimal symptoms (48%)	• Composition of the clusters was not consistent across analytic methods
Roiland, R. A.[66]	192 U.S. older adult breast cancer survivors	Cross-sectional Baseline data Symptom Bother Scale (37 items)	EFA, CFA SEM	1. Musculoskeletal: ache, stiffness, pain, joint pain, weakness, fatigue 2. Neurocognitive: balance, dizziness, memory problems, concentration 3. Dryness: dry skin, itching, dry mouth, thirst, shortness of breath	• 7-factor solution from EFA had adequate fit in CFA • All 7 clusters were associated with increased depression and poorer quality of life

				4. Urinary: incontinence, increased urination, decreased sex drive, irritated eyes 5. Circulatory: hand-foot swelling, taste or smell changes, hair thinning or loss, constipation, lymphedema, numbness 6. Sleep: frequent wakening, early wakening, difficulty falling asleep, vaginal discharge 7. Hormonal: mood swings, depression, anxiety, nightmares, hot flashes, headaches, vaginal dryness	
Wikman, A. [67]	402 Swedish patients with esophageal cancer	Cross-sectional EORTC QLQ-OES-18 completed 6 months after surgery	PCA, HCA	PCA and HCA solutions were identical except diarrhea formed a single symptom cluster using HCA; PCA solution was accepted. 1. Fatigue/pain—fatigue, pain, insomnia, dyspnea 2. Reflux/cough—dry mouth, taste changes, cough, reflux 3. Eating difficulty—appetite loss, dysphagia, eating difficulty, nausea-vomiting	The reflux/cough and eating difficulty symptom clusters were associated with increased risk of mortality

Table 5. Empirical Identification of Symptom Cluster Subgroups

Authors	Sample	Design	Method	Subgroups	Covariates/Patterns/Outcomes
Dirksen, et al. [68]	84 U.S. men with prostate cancer treated with radiotherapy	Longitudinal Pre-treatment, post-treatment Validated scales Cluster: fatigue, insomnia, pain, depression, anxiety, treatment-related (sexuality, urinary, and bowel symptoms)	Latent Class Analysis (LCA)	Pre-treatment groups: 1. Resilient (45%)—all low symptoms 2. Adjusted (41%)—high treatment-related symptoms; low insomnia, depression, anxiety 3. Distressed (4%)—All high symptoms 4. Emerged (10%)—High fatigue, depression, anxiety; low treatment-related symptoms Post-treatment groups: • Groups 1-3 had similar results • Group 4 changed to "Impacted" (5%)—high pain, insomnia, depression, urinary, bowel symptoms	• All men in the emerging group before treatment moved to another group (66% moved to Distress). • Among those whose group changed, there was a greater probability of changing to a group with higher symptom levels.
Doong, et al. [69]	398 U.S. women with breast cancer about to undergo surgery	Cross-sectional Pre-surgery Validated Scales Cluster: fatigue, pain, sleep disturbance, depressive symptoms	Latent Class Profile Analysis (LCPA)	1. All low symptoms (61%) 2. All high symptoms (7%) 3. Low pain, high fatigue (32%)	• Rare alleles of cytokine genes (IL6 rs2069845, IL13 rs1295686, TNFα rs1800610) had increased odds of being in the all-high symptoms subgroup.
Franceschini, et al.[70]	140 Brazilian Lung cancer patients	Cross-sectional EORTC QLQ-C30; symptoms selected for anlaysis: fatigue,	HCA	1. Mild symptoms (60%) 2. Moderate symptoms (28%) 3. Severe symptoms (12%)	• Subgroups with more severe symptoms had poorer quality of life

		pain, insomnia, depression			
Husain, et al. [71]	221 U.S. patients with advanced cancer	Longitudinal Study entry, weeks 2, 4, 8, 12 ESAS	Cluster Analysis	1. High-- tired; Moderate-- drowsy, appetite, wellbeing, pain, depression, anxiety (25%) 2. High-- tired; Moderate— drowsy appetite, wellbeing; Low—pain, depression, anxiety (31%) 3. Low—tired, drowsy, appetite, wellbeing, pain, depression, anxiety (44%)	• Subgroup membership predicted quality of life over time • Grouping by symptom cluster profiles did not add predictive value to a widely used measure of performance status in palliative care
Kim, et al. [72]	282 U.S. breast cancer patients treated with chemotherapy or radiotherapy	Longitudinal Pre-treatment, during treatment, end of treatment Some validated scales, some single items Cluster: Depressed mood, cognitive disturbance, fatigue, insomnia, pain	HCA at each time point Logistic regression	Pre-treatment 1. All low symptoms 2. High fatigue, low pain 3. High pain 4. All high symptoms During-end of treatment 5. High depressed mood, cognitive disturbance 6. High fatigue, insomnia	• Subgroup membership changed substantially across time except for group 1. • Subgroup 4 (reference group) differed from the other groups on baseline performance status, symptom burden, and treatment modality; this pattern was consistent across time.
Kim, et al. [73]	282 U.S. breast cancer patients treated with chemotherapy or radiotherapy	Longitudinal Pre-treatment, during treatment, end of treatment Some validated scales, some single items Cluster:	HCA using symptom severity scores across three time points Logistic regression	1. Gradually increasing symptoms (26%) 2. Constantly low symptoms (37%) 3. Dramatic increase and decrease of symptoms (14%) 4. Constantly high symptoms (13%) 5. Initially high symptoms with dramatic decrease (10%)	• Antecedents that distinguished group 4 (reference group) from other groups: baseline performance status, previous treatment, and education • Subgroup 4 had worse functional limitations than other groups

		Depressed mood, cognitive disturbance, fatigue, insomnia, pain			
Liu, et al. [74]	76 U.S. women with breast cancer being treated with anthracycline-based chemotherapy	Longitudinal: Pre-treatment, during each treatment cycle for 4 cycles (7 time points) Validated scales Cluster: fatigue, sleep disturbance, depression	Mixed effects model Independent variables: SCI Dependent variables: individual symptom scores	Symptom Cluster Index (SCI) groups based on scale cut-offs: • SCI0: no symptoms (20%) • SCI1: 1symptom (28%) • SCI2: 2 symptoms (56%) • SCI3: 3 symptoms (24%).	• Subgroups with higher SCI prior to treatment had worse symptoms during treatment compared with lower SCI groups • Subgroups did not differ by demographic or clinical factors
Reyes-Gibby, et al. [75]	599 U.S. newly diagnosed lung cancer patients	Cross-sectional Prior to treatment Single items: Cluster: Pain, depressed mood, fatigue	HCA Logistic regression	1. Severe symptoms (16%) 2. Low intensity symptoms (30%) 3. High pain; low depressed mood, fatigue 4. High fatigue; low depressed mood, pain 5. High fatigue depressed mood; low pain	Comparison of subgroups 1 and 2: Additive effect of 5 alleles predicted membership in high symptom group controlling for disease stage and sex: • ENOS -1474 T/A • IL1β T-31C • TNRR2 Met^{196} Arg • PTGS2 exon10+8731>C • IL1Orβ Lys^{47} Glu
Sanford, et al.[76]	80 U.S. women with breast cancer being treated with chemotherapy	Longitudinal: Pre-treatment, cycle 4 day 1, 6 months later Validated symptom scales Cluster: fatigue, sleep, depression, anxiety, cognitive impairment	Correlation; Mixed effect models	SCI groups based on scale cut-offs: • SCI0 (22%) • SCI1 (28%) • SCI2 (26%) • SCI3-5 (24%)	• Fatigue, depression, cognitive impairment: For each symptom, SCI groups had similar trajectories with symptoms worsening during treatment. • Sleep: There was no change in sleep within subjects or between groups. • Anxiety: SCI groups had similar trajectories with anxiety improving over time. • Higher SCI scores predicted poorer quality of life.

Starkweather, et al.[77]	128 U.S. women with breast cancer	Cross-sectional 4 weeks after breast surgery before chemotherapy Validated scales Cluster: fatigue, depression, pain	Cut-off scores, extreme discordant subgroup analysis, median spit	Composite score: comparison of groups with scores in the top and bottom 20% of the sample Extreme discordant scores: all symptoms above cut-off	• Using composite scores, high and low symptom groups differed on IL6 and IL7 • Using discordant scores, groups differed on IL7 • Using median split, groups differed on IL4 and IL5.

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