Review Article

Symptom Clusters in Patients With Advanced Cancer: A Systematic Review of Observational Studies

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Abstract

Context. Advanced cancer patients typically experience multiple symptoms, which may influence patient outcomes synergistically. The composition of these symptom clusters (SCs) differs depending on various clinical variables and the timing and method of their assessment.

Objectives. The objective of this systematic review was to examine the composition, longitudinal stability, and consistency across methodologies of common SCs, as well as their common predictors and outcomes.

Methods. A search of MEDLINE, CINAHL, Embase, Web of Science, and PsycINFO was conducted using variants of symptom clusters, cancer, and palliative care.

Results. Thirty-three articles were identified and reviewed. Many SCs were identified, with four common groupings being anxiety-depression, nausea-vomiting, nausea-appetite loss, and fatigue-dyspnea-drowsiness-pain. SCs in most cases were not stable longitudinally. The various statistical methods used (most commonly principal component analysis, exploratory factor analysis, and hierarchical cluster analysis) tended to reveal different SCs. Different measurement tools were used in different studies, each containing a different array of symptoms. The predictors and outcomes of SCs were also inconsistent across studies. No studies of patient experiences of SCs were identified.

Conclusion. Although the articles reviewed revealed four groups of symptoms that tended to cluster, there is limited consistency in the way in which SCs and variables associated with them are identified. This is largely due to a lack of agreement about a robust, clinically relevant definition of SCs. Future research should focus on patients' subjective experience of SCs to inform a clinically relevant definition of SCs and how they are managed over time. J Pain Symptom

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Symptom clusters, advanced cancer, palliative care

Introduction

It is well established that patients with incurable cancer typically experience multiple symptoms, consequently suffering a high symptom burden.[1,2] Recent literature in symptom management has emphasized a shift of focus from treating single symptoms to managing the dynamic nature of multiple symptom constellations.[3,4] However, currently, there is no consensus on the definition of "symptom clusters" (SCs), either conceptually or methodologically, in research and clinical practice. A commonly used definition of SCs is two or more concurrent and interrelated symptoms that occur together, with a high degree of predictability.[5,6] Symptoms within a cluster may group together in a nonrandom fashion but do not require a common etiology.[7,8] Furthermore, SC composition may or may not be stable throughout the disease course, although some authors have proposed a refinement in the definition of SCs to include stability as a necessary aspect.[9,10]

There is a lack of consensus on what SCs exist in the advanced cancer population, with SCs identified by different studies varying widely.[3,5] SCs are associated with a variety of disease, demographic, and biological variables, which may or may not explain a shared underlying mechanism. Some clusters may appear only in patients with a specific cancer location (e.g., eating and speaking problems in patients with head and neck cancer) or after specific treatments (such as fatigue, hair loss, and nausea associated with some types of chemotherapy), whereas others may only appear in patients near to death. There have been two literature reviews to date examining multiple symptoms in advanced cancer.[7,8] Both reviews highlighted significant challenges in drawing definite conclusions about relationships between and among multiple symptoms for this population because of significant methodological and conceptual variation among studies. These reviews did not examine the longitudinal stability of SCs in advanced cancer, and to date, no reviews have explored whether SCs remain consistent across different statistical methodologies, what the predictors and outcomes of SCs are, and what the experiences of SCs are in patients with advanced cancer.

Validation of the concept of SCs is difficult because assessing symptom interrelationships presents considerable methodological challenges. SC composition, consistency, and stability vary widely depending on a host of measurement factors, including the optimal assessment tool (long vs. short), the most clinically relevant symptom dimensions (prevalence vs. severity or distress caused), the optimal analytical method to derive the cluster, the optimal statistical "cutoff" points to define SCs, and the optimal timing of assessment. Quantifying the nature of clusters over time requires the researcher to reach congruency between the analytical method, statistical assumptions, and theoretical frameworks used to define SCs.[9]

In addition, longitudinal study designs are clearly required to investigate stability of clusters over the illness trajectory and the underlying mechanisms as to why SCs differ over time.[11] The temporal variability in symptom interrelationships for patients with advanced cancer limits the accuracy of SC profiles derived cross-sectionally.[9,12,13] For example, Lasheen et al.[12] found that hospice patients with advanced cancer display daily fluctuations in symptoms, with the only consistent symptom being depression, which predicted greater symptom burden and more severe symptoms. Factors such as variation in measurement timing, the number of symptoms included in an analysis, and the inclusion of multiple items to measure the same construct in symptom assessment can bias the generalizability of SCs over time.[9,14] Such variability and incongruities in the measurement, composition, and longitudinal stability of identified SCs have been argued to