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Cancer Symptom Cluster Management

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Abstract

Objectives—To discuss the importance of cancer symptom clusters in clinical practice, review evidence for symptom cluster interventions, and make recommendations for symptom cluster identification, patient education, and management in clinical practice.

Data Sources—Primary research and review articles identified through CINAHL, PubMed, and PsycINFO databases.

Conclusions—Several studies have investigated interventions for multi-symptom management, or have evaluated the secondary effects of a single-symptom intervention on related symptoms. To date, only five studies have tested an intervention designed to manage a specific cancer symptom cluster. Those studies used non-pharmacologic approaches (psycho-education, cognitive-behavioral strategies, and acupressure) to address the pain, fatigue, and sleep disturbance symptom cluster, or the respiratory distress symptom cluster with some initial evidence of success. Further development and efficacy testing of symptom cluster interventions is needed.

Implications for Nursing Practice—Clinical practice can be guided by knowledge of individual and multi-symptom management, and clinical judgment regarding possible etiologies of cancer symptom clusters. Clinicians should be aware of co-occurring symptoms in their patients, educate and involve patients in identifying symptom clusters and aggravating / alleviating factors, and coordinate treatment recommendations using strategies that are likely to be beneficial across symptoms.

Keywords

Symptom cluster; symptom management; clinical practice; therapeutics; patient education

Cancer clinicians have long understood that patients experience multiple symptoms throughout the course of their illness and treatment. Research demonstrates that these symptoms are often concurrent, with patients experiencing 8 or more symptoms at a given time.[1–2] Over the last decade, investigators have documented relationships among subsets of concurrent symptoms, and identified various “symptom clusters”.[3–5] In seminal publications addressing the concept of symptom clusters, scientists raised questions about the potential importance of clustered symptoms including possible cues about the underlying disease, response to treatment, prognosis, and quality of life.[6–8] More recently, investigators have begun to explore and test hypotheses about underlying etiology of specific symptom

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clusters.[9–10] Few studies, however, have addressed targeted symptom cluster management and implications for clinical practice. The purpose of this paper is to describe the importance of cancer symptom clusters in clinical practice, review evidence for symptom cluster interventions, and make recommendations for symptom cluster identification, patient education, and management in clinical practice.

Cancer Symptom Clusters in Clinical Practice

A number of cancer symptom clusters have been identified in research, using statistical analysis to identify relationships among symptoms. Some of these same symptom clusters are commonly observed in clinical practice. For example, a gastro-intestinal symptom cluster comprising nausea and vomiting, often with lack of appetite has been among the most widely identified and addressed clinical symptom clusters in cancer care.[3,5,11–13] The psychoneurological symptom cluster including concurrent pain, fatigue, and sleep disturbance, often with mood disturbances of anxiety and / or depression is described in the cancer symptom cluster literature and is also evident in practice, as these symptoms are among those most frequently reported by patients.[5,14–15] Investigators have also identified a respiratory symptom cluster including co-occurring breathlessness, fatigue, anxiety, and cough, particularly in patients with lung cancer.[13,16]

Other symptom clusters, each with slightly different co-occurring symptoms, may appear in data analyses, but are less evident or consistent in the clinical setting. It is likely that different symptoms co-occur based on a combination of factors such as the underlying cancer diagnosis and stage, the treatment modalities employed, and patient characteristics such as presence and type of comorbidities, psychosocial variables (e.g., resilience, social support) and biological context (e.g., genetic or microbiome characteristics). Cancer clinicians may be in the best position to identify the co-occurring and related symptoms that cluster in their unique patient populations, and those most relevant to their practice.

Importance to Clinical Practice

The science of symptom clusters and its application to practice should be important to clinicians for three central reasons. First, evidence indicates that symptom clusters warn of negative outcomes such as depression, functional or role limitations, poorer quality of life, and mortality.[17–19] Ignoring symptom clusters may jeopardize important patient health outcomes. Second, knowledge of symptom clusters allows for more thorough symptom assessment. If clinicians are aware of symptoms that typically co-occur, then when a problematic symptom is identified through standard symptom assessment procedures, clinicians can anticipate and probe further into other likely related symptoms. This may result in more efficient use of limited patient-provider time and potentially uncover symptoms that might otherwise have been overlooked. Third, recognizing the co-occurrence of specific symptoms creates the possibility of more efficient symptom management by targeting the cluster of symptoms with a single treatment approach.

Historically, the typical approach to cancer symptom management has been to prescribe an intervention or suggest several potential intervention strategies based on each individual

symptom reported. Thus a patient with co-occurring pain, fatigue, and sleep disturbance may be prescribed an opioid for pain, be given suggestions for exercise or energy conservation strategies for fatigue, and receive sleep hygiene training to improve sleep. This “single symptom” approach results in complicated self-management as patients and families attempt to balance multiple scheduled and PRN medications, implement behavior change, and attempt to master cognitive coping strategies and/or physical interventions. Barsevick[7] initially described the potential of “crossover” interventions; that is, treatment strategies that have been shown to benefit more than one symptom comprising the cluster. Selection of education and management strategies that are coordinated across multiple symptoms could simplify self-management.

The nature of the relationships among clustered symptoms can have important consequences for coordinating treatment strategies to best manage the symptom cluster. Williams[20] identified three different ways in which clustered symptoms may be related: 1) through a shared underlying etiology, 2) through a single “trigger” symptom that causes the development or exacerbation of other symptoms, and 3) through side effects of symptom treatments that cause other symptoms. One of the main foci of current symptom cluster science is exploring potential common biological, psychological or social mechanisms underlying the cluster that may serve as potential targets for treatment. For example, investigators have hypothesized that neuro-inflammation causes co-occurring symptoms of fatigue, sleep disturbance, loss of appetite, mood disturbance and cognitive difficulties.[21] Interventions that attenuate the inflammatory response may reduce severity of the symptom cluster. Other authors have suggested targeting the direct effects of cancer treatment (e.g., chemotherapy induced disruption of GI mucosa).[22] A treatment approach that helps maintain the integrity of GI mucosa may reduce co-occurring symptoms of indigestion, bloating, and diarrhea. In some symptom clusters, it appears that a single symptom causes the others. For example, pain may wake a person from sleep, and result in increased daytime fatigue; thus, treating the pain may resolve the related symptoms. Similarly, treatment for a single symptom may produce side effects that become a symptom cluster (e.g., opioid medication causes co-occurring nausea and constipation). In such cases, use of an alternative or modified treatment strategy for pain may eliminate the symptom cluster. Given these different pathways, a variety of approaches have been tested in the management of co-occurring symptoms.

Evidence for Management of Multiple Symptoms

Multi-symptom interventions

Studies that evaluate interventions designed to treat multiple symptoms pre-date the focus on cancer symptom clusters. Numerous psycho-educational and behavioral interventions have been developed and tested to help patients understand their cancer and its treatment and to empower them to report symptoms and engage in a variety of self-management behaviors targeted to individual symptom experiences.[23–26] Similar web-based applications have been developed, providing symptom monitoring and tailored self-management information for control of problematic symptoms.[27–28] Yet another group of studies have focused on clinical programs of palliative or supportive care, in which a clinical team routinely assessed

symptoms and provided treatment advice or referral for management of the symptoms reported.[29–32] Systematic reviews of these multi-symptom interventions demonstrated mixed results with regard to symptom outcomes. Symptom interventions using patient education and self-management coaching resulted in symptom reduction in five of nine trials; while only one of five studies of early palliative care programs reported improvements in symptom management compared to control conditions.[33–34] In general, these studies did not attempt to treat a specific symptom cluster, nor did they focus on a common underlying etiology across the symptoms experienced. Nonetheless, this work demonstrates the range of concurrent symptoms reported, and patients' need to cope with multiple symptom management activities.

Secondary effects of single symptom interventions

A number of investigators have taken the approach of testing the effect of an intervention on a single target symptom (primary outcome) and evaluating its secondary impact on patients' overall symptom burden, or on specific related symptoms. Studies testing interventions such as exercise (e.g., walking, Qigong), massage, and psychological strategies (e.g., guided imagery, virtual reality) have evaluated effects on overall symptom burden or symptom distress.[35–40] Secondary effects of physical symptom interventions on related psychological outcomes are also common. For example, changes in anxiety, mood, and sleep have been evaluated as secondary effects of interventions to reduce hot flash severity.[41–42]

A select subset of these studies has targeted co-occurring symptoms as documented components of a symptom cluster. When one symptom is observed or theorized to influence other symptoms, it is logical to evaluate the impact of a single symptom intervention on other downstream clustered symptoms. Barsevick and colleagues[43] conducted a randomized controlled trial of an energy conservation, activity pacing, and sleep management intervention to treat fatigue and sleep disturbance in patients receiving chemotherapy. The investigators tested the secondary effect of the intervention on pain and depression because the four symptoms clustered, and the investigators hypothesized that pain and depression were negatively influenced by fatigue and sleep disturbance. Other investigators have hypothesized causal effects of insomnia on fatigue and have measured secondary effects of insomnia interventions on the clustered symptom of cancer-related fatigue.[44–46]

Evidence for Management of Symptom Clusters

Multi-symptom interventions with results analyzed as symptom clusters

Given the growing emphasis on cancer symptom clusters, a new approach to testing multi-symptom interventions involves identification of statistical symptom clusters as part of the analysis plan. Two such examples were found in the literature. In these studies multiple symptoms were assessed at baseline (pre-intervention) and were analyzed to identify symptom clusters; then the effects of the intervention were evaluated on those symptom clusters. Jarden and colleagues[47] tested a multi-modal symptom management intervention using structured exercise, relaxation training, and individual psychosocial support in hospitalized patients recovering from hematopoietic stem cell transplant. They used principal component analysis to identify symptom clusters among the 21 physical, affective,

and cognitive symptoms assessed at study entry. Following intervention delivery, the investigators measured changes in the intensity of the symptom clusters weekly during hospitalization and at 3- and 6-month follow-up points. Compared to a usual care control group, there were improvements in gastrointestinal (nausea, vomiting, stomach pain, loss of appetite, diarrhea), cognitive (diminished concentration, memory problems, fatigue), functional (muscle aches and joint aches) and mucositis (mouth pain, throat pain, and difficulty swallowing) symptom clusters in the treatment group, but no improvement in an affective (nervousness, anxiety, and stress) symptom cluster.

Lengacher and colleagues[48] used a similar approach to test a mindfulness-based stress reduction and group support intervention in women who had completed treatment for early stage breast cancer. Participants were randomized to the experimental intervention group or usual care control group. The team used hierarchical cluster analysis to identify symptom clusters in the 13 symptoms assessed at baseline and then evaluated changes in these clusters at post-intervention data collection points. No between group differences were observed in symptom cluster severity including gastrointestinal (nausea, vomiting, lack of appetite, dry mouth, shortness of breath, and numbness), cognitive-psychological (distress, sadness, difficulty remembering, and pain), and fatigue (fatigue, disturbed sleep, and drowsiness) symptom clusters.

Interventions targeting specific symptom clusters

In her 2007 review of clinical management of symptom clusters, Williams[20] noted that “no reports currently exist in the oncology literature of studies that have tested…interventions for formally identified symptom clusters” (pg. 118). In the subsequent near decade, a small number of investigators have taken steps to address this gap in knowledge. To date, there have been five studies that tested an intervention designed to treat a specific symptom cluster. A summary of study characteristics is provided in Table 1. Two studies tested interventions for a respiratory symptom cluster, and three targeted the pain, fatigue, and sleep disturbance symptom cluster. In all but one of the studies, eligibility criteria required a minimum symptom cluster threshold (all symptoms in a previously determined cluster present, and with a certain degree of bother or severity), to qualify for study participation.

Yorke and colleagues[49] studied the feasibility of a respiratory distress symptom cluster intervention among adults with lung cancer who were experiencing co-occurring breathlessness, cough, and fatigue. Using a randomized controlled design, 107 patients were assigned to either usual care or usual care plus the respiratory distress symptom cluster intervention (RDSI). Components of the RDSI included (1) written information about the symptom experience, communication strategies, and fatigue management strategies, and training in (2) diaphragmatic breathing and calming exercises, (3) strategies to ease coughing, and (4) acupressure points selected to affect all three clustered symptoms. Training was delivered in two 1-hour sessions conducted in-person over a 4-week period. Outcomes were assessed at baseline, 4- and 12-weeks. Sixty-eight percent of participants provided follow-up data, and those who stayed on study reported daily or weekly use of the intervention components. No significant differences in dyspnea, cough, and fatigue were reported between the RDSI and usual care groups. Observed within group reductions in

symptom severity in the RDSI group led the investigators to suggest that the intervention is feasible, has promise, and merits further testing in a trial adequately powered to detect between group differences in symptom cluster change.

Chan, Richardson, and Richardson[16] tested the efficacy of a psycho-educational intervention for the symptom cluster of breathlessness, fatigue, and anxiety in patients with advanced lung cancer. Participants were not required to experience the symptom cluster upon recruitment, but were expected to develop the symptoms during a course of palliative radiation therapy. One-hundred forty participants were recruited prior to initiation of radiation, and were randomly assigned to the psycho-educational intervention or usual care. The intervention included preparatory information, discussion of the symptom experience, recommendations for self-care strategies, and training in progressive muscle relaxation, and was delivered in a single 40-minute session provided the week before starting radiation therapy. A booster session was provided 3 weeks later. Outcomes were measured at baseline, and at 6- and 12-weeks after initiation radiation therapy. Patterns of change in the symptom cluster, as well as changes in individual symptoms of breathlessness, fatigue, and anxiety, were significantly better in the treatment group compared to the control group from baseline to week 6. Change in symptom cluster score from baseline to week 12 did not differ between groups. These findings suggest potential benefit of the symptom cluster intervention, particularly during the course of radiation therapy, when treatment-related symptoms are exacerbated.

Yeh, Chien, Lin, Bovbjerg, and van Londen[50] studied the feasibility of an auricular acupressure symptom cluster intervention in women with breast cancer experiencing co-occurring pain, fatigue, and disturbed sleep. Thirty-one adults who had completed treatment or who were receiving adjuvant therapy for breast cancer were randomly assigned to sham or true acupressure. Treatment was delivered weekly, over a period of 4 weeks. Participants had seeds placed on acupressure or sham points once a week and were instructed to apply pressure to the seeds 3 times a day for 5 days, with 2 days off treatment each week. Of the 31 patients randomized, 81% completed study, and had 85% or greater adherence to daily acupressure practice. Within the true acupressure group, clinically significant reductions (≥ 30%) were reported in all 3 clustered symptoms, but did not differ significantly from sham acupressure in this feasibility trial. The investigators concluded that further investigation is necessary in an adequately powered trial.

In two separate trials, Kwekkeboom and colleagues[51–52] first demonstrated feasibility, then conducted a pilot randomized controlled trial, of a cognitive-behavioral symptom cluster intervention among adults experiencing co-occurring pain, fatigue, and sleep disturbance during treatment for advanced (metastatic or recurrent) cancer. In the pilot RCT, 86 patients were randomized to the cognitive-behavioral intervention or a waitlist control group. The cognitive-behavioral intervention provided information about the symptom cluster and training in the use of relaxation, guided imagery, and pleasant distraction strategies. Training was delivered in a single 30-minute session on a day when the participant was receiving treatment, with the expectation that symptoms would worsen over the subsequent 2 weeks. Outcomes were measured at baseline and 2-weeks. Within group improvement in the clustered symptoms was documented at the time the cognitive-behavioral strategies were

used in both studies. Between group differences were demonstrated in symptom cluster severity at 2-weeks, with significantly lower symptom cluster severity in the intervention compared to wait list control group. A larger randomized controlled trial to establish efficacy of the cognitive-behavioral symptom cluster intervention is currently in progress.

Given the small number and early stage of trials focused on managing specific symptom clusters, significantly more research is needed. There is preliminary evidence for strategies that may be useful in two symptom clusters – a respiratory distress symptom cluster, and the symptom cluster of pain, fatigue, and sleep disturbance. Populations studied have been limited primarily to those with lung cancer and / or those with advanced disease. Four of the five studies reviewed here identified a shared mechanism among the clustered symptoms (e.g., stress) or identified a treatment strategy that could simultaneously impact all clustered symptoms (e.g., acupressure, cognitive-behavioral strategies) and thereby simplify symptom self-management. As investigators learn more about actual or potential shared mechanisms underlying a symptom cluster, interventions should be tested that target the mechanism, and should clearly specify if the intent is to prevent a symptom cluster from emerging or to diminish the intensity and distress of an existing symptom cluster. It will be important for researchers to consider new symptom clusters and mechanisms as cancer treatment selection evolves from being driven by organ system (e.g., colorectal cancer) to molecular target (e.g., KRAS mutation). As evidence for symptom cluster interventions grow, researchers also need to be mindful of individual differences among patients, and engage in efforts to tailor symptom cluster interventions to individual psychosocial and biological characteristics.

Practice Recommendations

While there is insufficient high-level empirical evidence to support formal guidelines for symptom cluster management, there is adequate theoretical basis and knowledge to make reasonable recommendations for clinical practice related to cancer symptom clusters. Cancer clinicians must approach their practice with the knowledge that symptoms co-occur, some are related, and that patients must manage multiple symptoms at any given point on the cancer trajectory. Several directions are proposed for symptom cluster identification, patient education, and intervention.

First, clinicians should be familiar with the symptom clusters likely to occur in the unique patient populations they treat. Clinical factors to consider in anticipating symptom clusters include cancer diagnosis, stage of disease, treatment approach, and personal factors that may exacerbate the symptom experience (e.g., age, common comorbidities). When commonly reported symptoms are identified, the oncology clinician can drill down to identify and further evaluate symptoms that co-occur and are related. This may lead to identification of a “trigger” or “sentinel” symptom. In addition to individual symptom assessments based on clinical expertise, a multidimensional symptom assessment tool should be used to routinely screen for symptoms to facilitate a comprehensive assessment and to identify co-occurring symptoms.[53]

Second, clinicians should use their critical thinking skills and knowledge of symptom science to identify a potential common etiology or temporal pattern to the clustered

symptoms. When co-occurring symptoms are identified, further inquiry as to the sequence of presentation or exacerbation of those symptoms, and factors that make each symptom worse or better may provide clues to the causes of the symptom cluster, and identify potential targets for intervention. If a typical cascade of symptoms can be identified, and it is plausible that the initial symptom triggers the others, clinicians may select a management strategy that prevents or minimizes the initiating symptom. Alternatively, if it appears that secondary symptoms occur as side effects of treatment for the initial symptom, the symptom cluster may be managed by changing the treatment approach for the initial symptom. If all symptoms emerge simultaneously, it is logical to suspect a shared underlying etiology.

Third, clinicians need to update their approach to patient and family education to include symptom clustering. Patients need to be aware that certain symptoms co-occur and are related to each other. Accurately anticipating the co-occurrence of symptoms will help patients prepare and perhaps be less distressed by the occurrence of symptom clusters.[54] Patients who are not aware of symptom clusters may assume that they are not tolerating treatment as well as they should or worry that they are not responding to treatment and that their disease is progressing. In order to best cope with overall symptom burden, patients need to understand shared symptom etiologies and how single symptoms or their treatment strategies may contribute to occurrence, worsening or improvement in related symptoms. This knowledge may help patients to prioritize among multiple self-management strategies.

The materials traditionally used as mainstays in educating patients and family members about disease, treatment strategies, and symptom management should also be updated to address symptom clustering. Widely used, publicly available cancer education materials largely address single symptoms (e.g., Pain Control: Support for People with Cancer,[55] Getting Help for Fatigue[56]). Thus, patients must sort through lists of recommendations for each symptom complicating self-management of multiple co-occurring symptoms. One exception is the symptom cluster (or symptom pair) of nausea and vomiting. Patient education materials frequently address the management of these symptoms concurrently, with a unified approach to the cluster. Moving forward, patient education materials should be revised to explain commonly co-occurring symptoms and aggregate treatments that may be beneficial to symptom clusters.

Similarly, clinicians should strive to organize self-management recommendations based on multiple (clustered) rather than single symptoms. That is, rather than teaching several single-symptom management strategies, clinicians should coordinate self-management instructions focusing on strategies that may be effective across multiple clustered symptoms. For example, Table 2 lists symptom management strategies recommended for individual symptoms, and identifies categories of treatments that may be effective across symptoms. In selecting treatments, clinicians should consider the range of symptoms reported and look for the smallest number of strategies that can effectively be applied to the symptom cluster.

Fourth, in managing symptom clusters, clinicians should consider implementation of non-pharmacologic as well as pharmacologic interventions. Nonpharmacologic strategies such as psycho-education, exercise, cognitive and behavioral strategies, and sensory / art therapies may be as beneficial as medications with fewer adverse effects that contribute to other

symptoms.[57] Their mechanisms of action may be more broadly applicable across symptoms than the narrow effects of many pharmacologic strategies; which may explain their dominance in trials of symptom cluster interventions. Patients and caregivers report a preference for simple non-pharmacologic interventions that are tailored to their beliefs and preferences, relevant to their specific needs, fit within their daily routine, are timed for delivery when symptoms are problematic, and have potential for immediate benefit.[58]

While focusing on symptom clusters and selecting a coordinated approach to their management may lead to more efficient symptom self-management for patients and families, clinicians must consider that symptoms may have multiple causal pathways. If a symptom cluster intervention targeted to one of the pathways provides only partial symptom relief, then additional interventions may need to be considered. In individualizing patient care, oncology clinicians must take into account the overall burden of the symptom cluster on the patient, as well as the patient's capacity and tolerance for multiple interventions.

Conclusion

The growing cancer symptom cluster literature and multi-symptom experience reported by patients demonstrate the prevalence of symptom clusters and their impact on patients. Intervention research targeting the management of specific symptom clusters, however, is still in its infancy. To date, only five studies have tested an intervention designed to manage a specific cancer symptom cluster. Those studies used non-pharmacologic approaches (psycho-education, cognitive-behavioral strategies, and acupressure) to address the pain, fatigue, and sleep disturbance symptom cluster, or respiratory distress symptom cluster with some initial evidence of success. Further development and testing of symptom cluster interventions is needed. Until stronger evidence is available and symptom cluster practice guidelines can be generated, cancer clinicians can facilitate improvement in symptom clusters by investigating and attempting to understand the symptom clusters that appear in the patients they care for, including identification of possible mechanisms, providing patient education about symptom clusters, and coordinating treatment strategies that target the suspected mechanism or that are effective across cluster component symptoms.

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Table 1

Intervention Studies Targeting a Specific Symptom Cluster

Authors	Design & Sample	Symptom Cluster & Eligibility	Treatment Groups	Cluster Mechanism	Treatment effect
Yorke et al.[49]	Feasibility RCT N=107 adults with lung cancer (No chest XRT or chemo in the last 4 weeks, or surgery in the last 6 weeks)	1. Breathlessness 2. Cough 3. Fatigue All symptoms present *and* report of being "bothered" by at least 2 of the 3 symptoms	Symptom Cluster Intervention • Written information on symptom experience, communication and fatigue management strategies • Controlled breathing technique • Cough easing technique • Acupressure Control • Usual care (breathlessness and fatigue information booklets)	Not specified - combined patient and clinician preferred therapies for individual symptoms and one with crossover potential (acupressure).	Within group improvement in breathlessness, cough, and fatigue Between group - no significant difference compared to usual care control
Chan, Richardson & Richardson,[16]	RCT N=140 patients aged ≥ 16 year old with lung cancer receiving palliative XRT	1. Breathlessness 2. Anxiety 3. Fatigue No requirement for experience of the symptom cluster (anticipated to emerge during the course of XRT)	Symptom Cluster Intervention • Written preparatory information and discussion of the symptom experience • Advice regarding self-care strategies • Relaxation (PMR) training and practice Control • Briefing regarding the XRT procedure • Discussion of side effects focusing on skin care • Optional group session on general care before and after XRT.	Physical or emotional stress as a common underlying etiology of all 3 symptoms.	Between group – significant difference in change in composite symptom cluster score from pre-treatment to week 6 of XRT, but not from pre-treatment to week 12.
Yeh et al.[50]	RCT N=31 patients with breast cancer currently off treatment or receiving adjuvant therapy	1. Pain 2. Fatigue 3. Sleep Disturbance All symptoms present in the last week *and* at least two rated ≥ 3 on a 0-10 severity scale.	Auricular acupressure •Seeds taped to points targeting pain, fatigue, and sleep disturbance Control •Sham acupressure with seeds taped to points unrelated to pain, fatigue, or sleep disturbance	Selection of acupressure points that may stimulate the brain to active reflex pathways to relieve multiple symptoms	Within group improvement in symptoms Between group - no significant difference compared to sham acupressure
Kwekkeboom, Abbott-Anderson & Wanta,[51]	One-group pre-post feasibility trial N=30 adults receiving chemotherapy or radiation for advanced (recurrent or metastatic) cancer	1. Pain 2. Fatigue 3. Sleep Disturbance All symptoms present in the last week *and* at least two symptoms (one must be pain) rated ≥ 3 on a 0-10 severity scale in the last 48 hours	Cognitive-Behavioral Intervention • Education about symptom cluster • Patient selection of guided imagery, relaxation, and distraction strategies (used daily)	Crossover strategies with evidence of efficacy for at least 2 of the 3 clustered symptoms.	Within group - no change in symptoms from baseline to week 2, but immediate reductions in all 3 symptoms at the time the cognitive-behavioral strategy was used.
Kwekkeboom, Abbott-Anderson, Cherwin, Roiland, Serlin & Ward,[52]	Pilot RCT N=86 adults receiving chemotherapy or radiation for advanced (recurrent or metastatic) cancer	1. Pain 2. Fatigue 3. Sleep Disturbance All symptoms present in the last week *and* at least two rated ≥ 3 on a 0-10 severity scale.	Cognitive-Behavioral Intervention • Education about symptom cluster • Patient selection of guided imagery, relaxation, and distraction strategies (used daily) Control	Crossover strategies with evidence of efficacy for at least 2 of the 3 clustered symptoms. All 3 symptoms influenced by patients' stress, perceptions of control, and expectation for outcome.	Between group - symptom cluster severity was lower in the treatment compared to waitlist control group at week 2.

Authors	Design & Sample	Symptom Cluster & Eligibility	Treatment Groups	Cluster Mechanism	Treatment effect
			• Usual care (clinician recommended education and symptom management strategies)		

RCT = randomized controlled trial; XRT = radiation therapy; PMR = progressive muscle relaxation

Table 2

Categories of Recommended Symptom Management Strategies Across Symptoms[a]

	Anorexia	Anxiety	Constipation	Depression	Diarrhea	Dyspnea	Fatigue	Hot Flashes	Nausea/Vomiting	Pain	Sleep/Wake Disturbance
Cognitive and / or behavioral strategies (e.g., activity pacing, relaxation, meditation)		X		X		X	X		X	X	X
Touch/body-based strategies (e.g., massage, acupuncture)		X					X		X	X	
Exercise (e.g., physical therapy, yoga, walking)	X	X	X	X			X			X	X
Nutrition or dietary changes	X		X		X	X	X		X		
Psycho-education, social support	X	X		X		X	X		X	X	
Sensory / Art therapies		X					X		X	X	
Anticonvulsants (e.g., gabapentin)								X	X	X	
Antidepressants		X		X						X	
Anxiolytics (e.g., lorazepam), sedatives / hypnotics		X				X			X		X
Corticosteroids	X								X	X	
Opioids						X				X	

[a]Based on National Comprehensive Cancer Network and Oncology Nursing Society Putting Evidence Into Practice (PEP) guidelines, treatments recommended likely to be effective. [http://www.nccn.org/professionals/physician_gls/f_guidelines.asp; http://www.ons.org/practice-resources/pep]