

A randomized clinical trial of energy conservation for patients with cancer-related fatigue.

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Barsevick, A.M., [W. Dudley](#), S. Beck, C. Sweeney, K. Whitmer, et al., A randomized clinical trial of energy conservation for patients with cancer-related fatigue. *Cancer*, 2004. 100(6): p. 1302-10.

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Abstract:

BACKGROUND

The efficacy of energy conservation and activity management (ECAM) for fatigue reduction and maintenance of functional performance has never been evaluated in adults with cancer who are undergoing treatment.

METHODS

A randomized clinical trial compared an ECAM intervention with a control intervention focused on nutrition. Individuals initiating chemotherapy, radiotherapy, or concurrent therapy for cancer were randomized to receive either the semistructured ECAM intervention ($n = 200$) or the control intervention ($n = 196$). Participants in each group participated in 3 telephone sessions with an oncology nurse during the first 5 weeks of treatment. Data on fatigue and limitation of functioning were obtained before cancer treatment and at two follow-up points that coincided with times of high fatigue for each type of treatment. The outcomes of interest included perception of fatigue and functional performance.

RESULTS

A repeated-measures analysis of covariance using the type of cancer treatment as a covariate revealed a significant study group-by-time interaction indicating that the ECAM group experienced a greater decrease in fatigue over time compared with the control group ($F_{2,544} =$

4.5; P = 0.01). The intervention was not associated with changes in overall functional performance.

CONCLUSIONS

Individuals who received the ECAM intervention derived a modest but significant benefit from it. To achieve a more robust clinical benefit from the intervention, it may be necessary to manage other key symptoms in addition to fatigue. Research is needed to examine symptom clusters or combinations associated with negative outcomes as well as combination strategies for symptom management.

Keywords: fatigue | symptom management | quality of life | symptom clusters | cancer

Article:

Fatigue has been described as the most frequent and distressing problem related to cancer and its treatment.^{1–4} It is known that fatigue interferes with quality of life regardless of diagnosis, treatment, or prognosis.^{5–9} There is evidence suggesting that cancer-related fatigue (CRF) has profound effects on a patient's ability to function in usual roles and activities,^{10–12} causes delays in treatment,¹³ lingers for months or years,^{9, 14, 15} and may be predictive of shorter survival in certain cancer populations.^{16–18} The prevalence of this symptom as well as its consequences identify it as a significant problem for patients with cancer who are undergoing treatment.

Although the problem of CRF has been well described, only two interventions aimed at managing CRF have been evaluated scientifically. Research has demonstrated that a regular program of sustained exercise reduced perceived fatigue in women with breast cancer and in individuals receiving high-dose chemotherapy (CTX).^{19–25} It also has been demonstrated that the management of anemia with recombinant human erythropoietin reduces perceived fatigue in patients with cancer.^{26–28} However, exercise is not indicated for patients with cancer who have bone metastases, suppressed immunity, low platelet counts, or fever.^{29, 30} In addition, sedentary individuals are unlikely to initiate and/or sustain a regular exercise program. Likewise, anemia management is appropriate only for individuals with low hemoglobin levels. Clearly, there is a need for research to identify additional approaches to the management of CRF.

The most common strategies selected by patients with cancer to manage fatigue include the reduction of activity and increased rest.^{31, 32} This approach to fatigue management is based on the misconception that CRF is like the fatigue experienced during times of health and, thus, is responsive to increased rest. Because CRF is not due to over-activity, it is unlikely that patients with cancer will benefit from reduced activity alone. However, it is possible that rest as a means

of conserving energy resources may enable an individual to continue participation in valued activities.^{3, 5, 28} The objective of the current research was to determine whether mastery and use of energy conservation and activity management (ECAM) skills is beneficial to patients with cancer in reducing perceived fatigue and improving perceived ability to function in usual activities.

Energy conservation is the deliberate, planned management of an individual's personal energy resources to prevent their depletion. The objective of energy conservation is to balance rest and activity during times of high fatigue so that valued activities and goals can be maintained. Taking additional rest periods is one energy-conservation strategy. Other strategies include priority setting, delegation, pacing oneself, and planning high-energy activities at times of peak energy.

Because energy conservation is a common sense activity, the Common Sense Model was used to guide the development and implementation of the ECAM intervention.^{33–35} The model proposes three stages of information processing regarding symptom management: representation, coping, and appraisal. In the representation stage, the individual gathers information to form a mental image of a symptom, including its identity, cause, pattern, controllability, and consequences. During the coping stage, the individual identifies and implements self-care strategies to manage the symptom. The third stage, appraisal, involves an evaluation of coping efforts and adjustment of coping methods and/or symptom representation based on the experience of symptom management. A focus group study supported the validity of the model as an organizing framework for understanding fatigue management in patients with cancer.³⁶

Information is essential to the development of an accurate representation or mental image of the problem of fatigue, and coping skills are essential in handling fatigue.³⁷ Based on the Common Sense Model, information is most effective when it addresses the components of a symptom representation that include what the symptom is, as well as the symptom's cause, pattern, controllability, and anticipated consequences.³⁸ Interventions also focus on the unique symptom presentation for an individual, his or her history and knowledge base, and the coping strategies with which he or she is familiar. Successful interventions correct faulty ideas, support new coping efforts, and generate new skills.

Most of the research on energy-conservation interventions has been conducted on populations with chronic illnesses other than cancer that are characterized by fatigue.^{28, 39–42} These include rheumatoid arthritis, multiple sclerosis (MS), pulmonary diseases, chronic fatigue syndrome, and

postpolio syndrome. A qualitative content analysis⁴⁰ of fatigue in individuals with chronic obstructive pulmonary disease and asthma and another qualitative study of individuals with MS³⁹ revealed that energy conservation was used commonly to manage fatigue in these populations.

A limited number of studies have provided evidence that energy-conservation interventions benefited individuals with chronic illnesses; however, those interventions involved a combination of approaches; therefore, it is not possible to isolate the effect of energy conservation alone. In addition, those studies had small samples, and some did not have a control group. A 9-hour, 6-week educational program that included energy-conservation information resulted in greater use of ECAM behaviors in an intervention group compared with a control group, although there was no effect on fatigue or functional status.⁴³ A 6-session support group followed by a 6-session energy-conservation course was tested in a repeated-measures design with 54 individuals who suffered from fatigue secondary to MS.⁴¹ The pattern of fatigue in that study demonstrated a larger decrease during the 6-week energy-conservation course than during the support group. These studies of noncancer populations provide some support for the usefulness of energy conservation to manage fatigue during chronic illness.

MATERIALS AND METHODS

Design

In the current study, a randomized clinical trial design was used to compare the ECAM intervention with a control intervention that was similar in terms of time and attention. A pilot study demonstrated that the ECAM intervention was acceptable and feasible for patients with cancer.⁴⁴ The study was conducted at two clinical sites: a university health science center (University of Utah [UU], Salt Lake City, UT) and a comprehensive cancer center (Fox Chase Cancer Center [FCCC], Philadelphia, PA). Individuals who were beginning CTX, radiotherapy (RT), or concurrent therapy for cancer were randomized to receive either the semistructured ECAM intervention ($n = 200$) or the control intervention ($n = 196$), which involved the distribution of information regarding a healthy diet.

Inclusion and Exclusion Criteria

Individuals were eligible if they were currently beginning treatment for breast, lung, colorectal, advanced prostate, gynecologic, or testicular cancer or lymphoma and if they planned to receive

≥ 3 cycles of CTX, 6 weeks of RT, or concurrent RT and CTX. Any prior treatment other than surgery was required to have been completed at least 1 month previously. Treatment was intended for cure or local control, and the interventions and questionnaires had to be delivered in English. Individuals were excluded if their treatment plan included stem cell transplantation, interleukins, interferons, or tumor necrosis factor or if the individual had chronic fatigue syndrome. Individuals also were excluded if they were enrolled in another study that involved a psychoeducational intervention or if they had overt evidence of psychiatric disorder. Another exclusion criterion was the initiation of treatment for anemia or depression during the previous 3 weeks, because these modifiable causes of fatigue²⁵ may have been confounded with the effect of the ECAM intervention.

Procedure

The Institutional Review Board (IRB) at each study site approved the research protocol in accordance with federal regulations. Informed consent was obtained from all study participants. Upon completion of the baseline questionnaires, participants were stratified by job status (working vs. nonworking), type of treatment (CTX vs. RT vs. concurrent therapy), and diagnosis (breast cancer vs. nonbreast cancer) to ensure equivalence of the experimental and control groups on these factors. Participants then were randomized to receive the ECAM intervention or the nutritional (control) intervention.

Participants in each intervention group participated in three telephone sessions with a specially trained oncology nurse. For patients who were receiving CTX or concurrent therapy, the intervention occurred during the first 3 weeks of treatment; for patients who were receiving RT, the intervention occurred during Weeks 3–5 of treatment. Baseline data on fatigue and limitation of functioning were obtained before the start of cancer therapy and at two follow-up points that coincided with times of high fatigue for each type of treatment. For individuals who were receiving cyclic CTX or concurrent therapies, follow-up questionnaires were administered 48 hours after the second and third CTX treatments, because it is known that fatigue is elevated at these times.⁴⁵ For individuals who were receiving RT, follow-up questionnaires were administered during the last week of treatment and 1 month after the completion of treatment, times that also are recognized as times of high fatigue.²

Interventions

The ECAM intervention was based on the tenets of the Common Sense Model.^{33–35} The intervention guided the participant through the three stages of information processing proposed

in the model.³⁸ Information was provided to aid in the formation of an accurate representation of the symptom of fatigue, guide the formulation and implementation of a plan for energy conservation, and appraise the effectiveness of symptom-management efforts. An interactive approach for intervention delivery was used that built on the individual's existing knowledge of energy-conservation strategies and unique responses to symptoms. A specific protocol and script were used, but the research nurse who delivered the intervention was trained to customize the protocol. For example, if the participant recognized the need to delegate activities but admitted difficulty doing so, then the nurse counselor would work on the problem of delegation.

In the first of three telephone sessions, which addressed the representation and coping stages of the model, individuals received information on CRF and learned energy-conservation skills that would assist in its management. For homework between sessions, participants completed a daily journal for 1 week to monitor fatigue, sleep, rest, activity, and other symptoms. They assessed their activity patterns by making a list prioritizing their usual activities. The journal and priority list provided the basis for the second session, during which the individual was assisted in creating an energy-conservation plan to manage valued activities and to minimize the interference of fatigue (the coping stage). In the third session, the individual evaluated and revised the plan (the appraisal stage). The planned length of the intervention sessions was 30 minutes each for Sessions 1 and 2 and 15 minutes for Session 3.

To protect the integrity of the experimental intervention, all interventions were conducted by telephone with staff located at FCCC. The use of a centralized staff minimized differences in the application of the experimental variable. Additional safeguards included 8 hours of counselor training, individual case supervision for the research nurses, and an examination of nurse adherence to key elements of the intervention. Nurse adherence in administering the key elements of the interventions, which was examined on a quarterly basis for 20% of cases using audiotapes of the interventions, consistently was > 90%, the standard set for this study.

The purpose of the control intervention was to control for the amount of time and attention received by the experimental group. It consisted of information on nutrition and a healthy diet. This content was chosen because it is of interest to patients with cancer and because it is somewhat relevant to fatigue but is believed to be of limited value for fatigue management during aggressive cancer treatment.⁴⁶ Information provided in the first session included a discussion on maintaining a healthy diet. For homework, the participant kept a dietary record for 24 hours. The second session consisted of a review of the dietary record and a discussion about vitamins. The third session consisted of a discussion about minerals and an evaluation of the helpfulness of the information provided. No therapeutic nutritional information or information on

symptom management was provided during the control intervention sessions. The three sessions were equal to the experimental intervention in terms of the amount of time spent with the individual (ECAM: average total time, 78 minutes; control: average total time, 72 minutes).

Measures

Because demographic and clinical information can influence the outcome of cognitive behavioral studies, relevant information was abstracted from the medical record or obtained from participants by questionnaire. The outcomes of this study included perception of fatigue and functional performance. Three scales were chosen to measure unique aspects of fatigue, which was the central variable of this study. The Short Form of the Profile of Mood States (POMS-SF)⁴⁷ contained a five-item adjective checklist that measures fatigue intensity during the past week; for example, exhausted was measured on a scale ranging from 1 (“not at all”) to 5 (“extremely”). A recent study established the validity and reliability of the fatigue scale in patients with cancer.⁴⁵ Cronbach alpha reliability for this sample was 0.89. The Schwartz Cancer Fatigue Scale (SCFS)⁴⁸ is a similar six-item adjective checklist with two component scores: Physical Fatigue and Mental Fatigue. The Physical Fatigue subscale was used (Cronbach alpha = 0.97). The General Fatigue Scale (GFS), which is a 7-item scale (Nail LM, Meek P, Barsevick A, et al. Unpublished data, 2002), was designed for the current study to capture fatigue impact at specific times, including fatigue today, on most days, in the past 48 hours, and in general. Two additional items addressed distress due to fatigue and its impact on daily activities (Cronbach alpha = 0.95). Evidence of validity of this scale includes sensitivity to change in activity levels ($P < 0.001$) and a factor analysis demonstrating a single factor.⁴⁹

Limitation of functioning in valued activities due to CRF was measured using the Functional Performance Inventory (FPI),⁵⁰ a 65-item scale with 6 subscales, including body care, household maintenance, physical exercise, recreation, spiritual activities, and social activities. Rating of items such as “going to sporting events or concerts” included “doing with no, some, or much difficulty” and “do not do so for health reasons.” Higher scores reflected better functioning. Reliability and validity have been demonstrated (Cronbach alpha for this sample = 0.91).^{51, 52}

RESULTS

Six hundred twenty-five individuals met the eligibility criteria to participate in the randomized clinical trial. Two hundred twenty-nine of these individuals did not enroll in the study. Reasons

for not enrolling included lack of interest (55%) lack of timely contact (22%), or a variety of other reasons (49%). Because of IRB concerns about protected health information, no demographic information was retained from individuals who did not enroll in the study. The majority of the sample was female (85%), Caucasian (91%), married (68%), and college educated (65%) (Table 1). Forty-four percent of the total sample received treatment with RT, 47% received CTX, and 9% received concurrent therapy. The most common diagnoses were breast cancer (71%) and lung cancer (16%) (Table 2).

Table 1. Patient Demographics (n = 396)

Characteristic	No. of patients (%)
Age (yrs)	
Mean ± SD	56.3 ± 12.5
Range	18–83
Gender	
Female	337 (85)
Male	59 (15)
Ethnicity/race	
Caucasian	361 (91)
Nonwhite	35 (9)
Education	
No college	125 (32)
College+	257 (65)
Unknown	14 (3)
Marital status	
Married	268 (68)

Characteristic	No. of patients (%)
Not married	119 (30)
Unknown	9 (2)
Work status	
Working	183 (46)
Not working	213 (54)
Study site	
FCCC	245 (62)
UU	151 (38)

SD: standard deviation; FCCC: Fox Chase Cancer Center (Philadelphia, PA); UU: University of Utah (Salt Lake City, UT).

Table 2. Clinical Characteristics of the Study Population ($n = 396$)

Characteristic	No. of patients (%)
Cancer diagnosis	
Breast	282 (71)
Lung	63 (16)
Lymphoma	24 (6)
Colorectal	16 (4)
Genital (endometrial, ovarian, prostate, testicular)	11 (3)
Stage (AJCC/UICC)	
0	25 (6)
I	120 (30)

Characteristic	No. of patients (%)
II	128 (32)
III	75 (19)
IV	35 (9)
Unavailable	13 (4)
Treatment	
Chemotherapy only	184 (47)
Radiotherapy only	176 (44)
Concurrent therapy	35 (9)

AJCC: American Joint Committee on Cancer; UICC: International Union Against Cancer.

Two hundred thirty-four individuals provided complete data on all 3 fatigue measures at all data points that were conducted; 162 individuals had missing data for at least 1 data point on at least 1 fatigue measure. These groups were compared with regard to intervention group assignment. Failure to complete all fatigue measures was unrelated to intervention group assignment (chi-square [1] = 1.6; P = 0.21). Thus, complete and incomplete cases were distributed evenly across both study groups.

Incomplete data from participants in the two intervention groups (ECAM vs. control) did not differ with regard to overall symptom burden (t , 1152 = 1.5; P = 0.12), baseline GFS score (t , 1148 = 0.65; P = 0.52), or Eastern Cooperative Oncology Group (ECOG) performance status (Mann–Whitney U = 3556; P = 0.35). However, without regard to intervention group assignment, participants who had incomplete data had higher symptom burden (t , 1384 = 4.22; P < 0.001) and poorer ECOG performance status compared with participants who had complete data (U test = 10591; P = 0.01). These findings suggest that in both intervention groups, patients who were in poorer health were more likely to have incomplete data.

Baseline equivalence between intervention groups, study sites, and cancer treatment groups was examined. Intervention groups (ECAM vs. control) were compared with regard to demographic and clinical factors using chi-square analysis and t tests to determine whether differences between the groups could be attributed to extraneous factors. Of particular interest were the three

stratification factors: diagnosis (breast cancer vs. nonbreast cancer), work status (working vs. not working), and treatment type (RT vs. CTX vs. concurrent therapy). Interventions groups did not differ with regard to any demographic or clinical factor, including diagnosis, type of cancer treatment, or work status. To establish the equivalence of participants from the two sites (FCCC vs. UU), similar analyses comparing demographic and clinical variables for the two sites were conducted. Several differences were noted. Participants at FCCC were more likely to be African American ($P = 0.01$), less likely to be treated with RT alone ($P = 0.03$), and more likely to receive concurrent therapy ($P = 0.03$). FCCC participants also tended to be slightly older ($P = 0.08$) compared with UU participants (mean age, 57 years vs. 55 years, respectively).

Because the type of cancer treatment may influence fatigue levels, baseline equivalence of fatigue for each cancer treatment group (CTX only, RT only, or concurrent therapy) also was examined. Individuals who were treated with RT alone were older ($P < 0.001$) compared with individuals who received concurrent therapy or CTX alone, as would be expected because of current standards of care. Likewise, participants who received RT alone had lower stage disease ($P < 0.001$) compared with participants in other cancer treatment groups, as expected.

Age, ethnicity, and type of cancer treatment were examined as potential covariates in the multivariate analysis comparing the efficacy of the interventions to manage fatigue and maintain functional performance. Age and ethnicity were unrelated to the study outcomes at follow-up, indicating their unsuitability as covariates. In a one-way analysis of variance (ANOVA), type of cancer treatment was associated with fatigue at the second follow-up point ($P < 0.001$), and type of cancer treatment was associated with functional performance at both follow-up points ($P < 0.001$). Post hoc analysis indicated that the mean scores for the RT group differed from the CTX and concurrent therapy groups; however, the latter two groups did not differ from one another. For use as a covariate, type of treatment was stratified into two groups rather than three: RT only versus CTX or concurrent therapy.

In the second step of the analysis, a manipulation check was conducted to determine whether the ECAM group used more energy-conservation behaviors taught during the intervention than the control group. At baseline and at both follow-up data points, participants in both study groups completed a 17-item checklist; 9 items referred to energy-conservation strategies (delegation, planning, pacing, etc.), and 7 items were unrelated coping behaviors (relaxation, aromatherapy, etc.). A repeated-measures ANOVA revealed that the ECAM group used significantly more energy-conservation strategies over time compared with the control group (Table 3). There was no difference between the intervention groups with regard to the use of non-energy-conservation behaviors. These findings indicate that the ECAM intervention influenced behavior in the

expected way: individuals who were taught energy conservation used these strategies more frequently than did individuals who were not taught ECAM.

Table 3. Means, Standard Deviations, F Tests, and P Values for Effects

Measure	Mean (SD)		<i>F</i> test (repeated-measures design)				
	Baseline	Follow-up 1 ^a	Follow-up 2 ^a	Cancer treatment	Time	Study group	Study group by time
ECAM	2.8	2.7	2.7	5.53 ^c	22.0 ^b	0.41	1.5
Control	2.7	2.7	2.6				

SD: standard deviation; ECS-A: Energy Conservation Strategies–Appropriate; ECS-NA: Energy Conservation Strategies–Not Appropriate; GFS-Total: General Fatigue Scale–Total; POMS-F: Profile of Mood States–Fatigue; SCFS-P: Schwartz Cancer Fatigue Scale–Physical; FPI-Total: Functional Performance Inventory–Total.

a Follow-up points 1 and 2 coincided with times of high fatigue for each type of treatment.

b $P < 0.01$.

c $P < 0.05$.

The final step of the analysis was to test the efficacy of the ECAM intervention using a repeated-measures analysis of covariance with type of cancer treatment controlled in the analysis. An intent-to-treat analysis was conducted in which all participants were evaluated as randomized, regardless of whether they had completed all three intervention sessions. The SAS mixed procedure restricted maximum likelihood method was chosen, because the current study involved repeated measures that were correlated and had changes in variability due to attrition.⁵³ Two hypotheses were tested: compared with the control group, the group that received the ECAM intervention would report 1) less fatigue over time and 2) less disruption of functional performance over time. Because three fatigue measures were used to examine different dimensions of the subjective experience of fatigue, each measure was examined in a separate repeated-measures ANOVA using cancer treatment type entered as a covariate. The significant study group–by-time interaction revealed that fatigue, as measured by the GFS, the POMS-F, and the SCFS-Physical scales, was significantly lower over time in the ECAM group ($P < 0.01$, $P < 0.05$, and $P < 0.05$, respectively) (Table 3). Because 3 fatigue measures were used, it may be argued that there is need for a correction of the alpha ($\alpha/3 = 0.017$) to guard against type 1 error; in this case, only the analysis involving the GFS would be statistically significant.

A similar analysis was conducted for the measure of functional performance (FPI-Total and each of the six subscales). The intervention was not associated with changes in overall functional performance or any of the six dimensions of functional status. Because of this incongruent result, we examined a single item from the GFS that described the impact of fatigue on usual activities. A repeated-measures ANOVA with type of treatment as a covariate revealed that the ECAM

group had significantly less disruption of usual activities compared with the control group ($P = 0.0008$).

Because of the disparity in terms of gender in the study population (85% females), additional analyses were conducted to examine gender differences in the effects of the intervention. First, gender was included as an independent variable in the repeated-measures ANOVA for all outcomes reported in Table 3; no main effect was observed, and the two-way and three-way interactions of interest were not statistically significant. Second, the analyses were conducted separately for male and female samples. For females, all of the significant interactions listed in Table 3 remained significant. For males, the interactions of interest did not attain statistical significance.

DISCUSSION

The results of the current study demonstrated a statistically significant difference over time in favor of the ECAM group. It is challenging to determine whether this was a clinically important difference with respect to a phenomenon that was expected to become worse due to cancer treatment. The goal of the ECAM intervention was to minimize the expected rise in fatigue. The pattern of scores was congruent with that goal, demonstrating a mean decrease in all fatigue measures for the ECAM group between the first and second follow-up data points compared with a slight increase for the control group. At least 1 empirical study was undertaken to determine clinically important changes in fatigue for patients with cancer;⁵⁴ however, that study's design allowed only for the detection of clinically important increases in fatigue 2 days after treatment. It is not known whether this criterion is applicable to decreases in fatigue as well. Dineen et al.⁵⁵ have indicated that the magnitude of perceived clinical significance may vary depending on the direction of the change. We observed that 10% more ECAM participants had improvement or no change in fatigue, whereas about 15% fewer ECAM participants had worsening fatigue over time compared with the control group. Future research should assess characteristics of responders and nonresponders to fatigue intervention. It also appears that development and testing of a stronger intervention are warranted. For example, a multifaceted intervention focusing on both fatigue and sleep disturbance may be indicated for this population. In addition, future research should address questions related to the perceived clinical usefulness of the intervention.

Overall, the ECAM intervention was acceptable and well tolerated; satisfaction, as measured in a previous pilot feasibility study,⁴⁴ indicated that most participants found that the intervention was

credible and helpful. Findings for the manipulation check demonstrated that participants who were taught energy-conservation strategies learned and used them over the course of the study.

The lack of a significant result with respect to the primary measure of functional performance was puzzling. A previous qualitative study³⁶ indicated that patients with cancer associate fatigue with significant decrements in functional performance. It is noteworthy that the single item on the GFS was significant, whereas the detailed FPI-Total was not. One difference between the two measures is that the GFS item addressed functional performance related to fatigue, whereas the FPI considered only how functioning was affected by “your health.” It is possible that patients with cancer viewed the FPI items in a broader context that was influenced by factors other than fatigue only, in effect diluting the connection between fatigue and functional performance.

There are several limitations to the study results we present here. Despite our best efforts to include a broad sample of cancer diagnoses, patients with breast cancer constituted the majority of the sample. The overrepresentation of females and patients with breast cancer limits our ability to generalize the results to both genders and to patients with other diagnoses.

Second, a substantial number of participants had missing measures, primarily due to medical complications. However, despite the fact that patients with incomplete data were in poorer health, there is no evidence of intervention group differences for patients who had incomplete measures with regard to baseline fatigue, overall symptom burden, or ECOG performance status. Because missing data were not related to group assignment, efficacy findings were not confounded by the inability of patients who were in poorer health to complete the data collection process.

The overall conclusion of the current study is that more research is needed to examine symptom clusters or combinations associated with negative outcomes as well as multifaceted strategies for symptom management.^{56, 57} Given et al.⁵⁸ have identified the symptom pair of fatigue and pain as a predictor of increased symptom burden. Our own research indicates that sleep disturbance is a prevalent problem that is likely to interact with fatigue. Specific behavioral interventions for sleep management may boost the overall effectiveness of fatigue and symptom management.

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