Efficacy of an Intervention for Fatigue and Sleep Disturbance during Cancer Chemotherapy

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Abstract:

Context- Multiple complex symptoms from cancer treatment can interfere with functioning.
Objectives- To evaluate the efficacy of an "energy and sleep enhancement" (EASE) intervention to relieve fatigue and sleep disturbance and improve health-related functional status.
Methods- Individuals receiving chemotherapy (CTX) were randomized to the EASE (*n* = 153) or a control intervention (*n* = 139). The EASE intervention included information and behavioral skills taught by an oncology nurse in three telephone sessions. The primary outcomes of fatigue, sleep disturbance, and functional status were measured before CTX, Day 4 after first treatment (baseline), and 43–46 or 57–60 days later (follow-up), depending on the CTX cycle length.
Results- The sample was primarily female (82%) and non-Hispanic white (89%), with mean age of 53.9 years. Fatigue and patient-reported sleep disturbance were elevated in both groups at baseline and follow-up. Actigraphy revealed that the total sleep time was almost eight hours, and sleep percent was greater than 85% for both groups at both time points (normal range). Physical functioning was diminished and at the same level as a sample with serious illness. Mental functioning was in normal range. A repeated-measures analysis of variance revealed no statistically significant group-by-time effects for fatigue, sleep disturbance, or functional status. Unemployed individuals showed greater benefit from the EASE intervention, reporting less pain and symptom interference.
Conclusion- Potential explanations include high variability and/or floor effect for fatigue, incorrect timing of measures, insufficient amount or dose of the intervention, and confounding effects of gender. Future research should consider screening for symptom severity and tailoring interventions.

Article:

INTRODUCTION

Individuals with cancer often deal with multiple complex symptoms during cancer treatment that can interfere with functioning in usual roles and activities. However, research has typically focused on the alleviation of single symptoms, such as pain, fatigue, sleep disturbance, and depression. [1,2] Research is needed to examine the efficacy of intervention for multiple symptoms and determine whether intervention intended for one symptom will influence the severity of other symptoms.

In the research presented here, four symptoms were chosen for consideration. Two symptoms—fatigue and sleep disturbance—were targeted for intervention; the other two—pain and depression—were selected for observation. Cancer-related fatigue was a focus of this investigation, because a previous clinical trial demonstrated that training in energy conservation strategies significantly reduced fatigue.[3] That study also showed that sleep disturbance was a significant problem during cancer treatment. Because sleep disturbance can increase fatigue, it was chosen for intervention in the current research. Two related symptoms, pain and depression, were chosen for evaluation in this research (but not targeted for intervention) because of a growing body of evidence linking them to cancer fatigue.[4,5,6,7] The study was designed to extend past research systematically and incrementally by examining the effect of an intervention on the target symptoms (fatigue and sleep disturbance) and exploring how the related symptoms (pain and depression) might be influenced by the intervention. Thus, the aim of the research was to test the efficacy of an "energy and sleep enhancement" (EASE) intervention on the primary outcomes of fatigue, sleep disturbance, and functional status and the secondary outcomes of pain and depression.

Past research has demonstrated that some symptoms influence other symptoms and have a negative effect on one or more symptom outcomes.[1,2] Given et al. provided evidence that specific symptoms (fatigue, sleep disturbance, and pain) had different effects on outcomes when one, two, or all three symptoms were present. In one study, individuals who reported both pain and fatigue reported more symptoms overall than those who reported either symptom or neither symptom.[8] In a separate analysis, pain, fatigue, and sleep disturbance were examined as predictors of functioning.[9] Compared with no pain, fatigue, or sleep disturbance, individuals who had one, two, or all three symptoms had incrementally greater risk of impaired functioning during cancer therapy. Testing a mediation model, Beck et al.[10] determined that pain influenced fatigue directly and also indirectly through its effect on sleep; this finding suggested that the use of better pain management to improve sleep could also decrease fatigue. The findings of these studies suggested that fatigue, sleep disturbance, and pain could be studied as a symptom cluster, because these symptoms tended to co-occur, and they influenced one another.

Research has suggested that depression is related to the other symptoms of interest (in this context, "depression" refers to "depressive symptoms," not a clinical diagnosis).[7,11,12,13,14,15,16] Some studies have demonstrated that depressive symptoms were influenced by other symptoms and changes in functioning. In a longitudinal study of outpatients with cancer, Williamson and Schulz[17] demonstrated that, as pain increased and restricted activity, depressive symptoms also increased. Another study of fatigue and depression in cancer patients undergoing treatment demonstrated a similar result: There was a direct relationship between fatigue and depression as well as an indirect relationship between the two symptoms through the influence of fatigue on functional status.[18] As fatigue increased and functioning in usual activities decreased, depressive symptoms increased. Because depressive symptoms have been associated with pain, fatigue, and functional status, it makes sense to examine these symptoms in the context of a symptom reduction intervention.

Only a few symptom management studies have examined multiple symptoms.[19,20,21] A comprehensive coping strategy intervention targeted to reduce pain, fatigue, nausea, and depression in breast cancer patients during autologous bone marrow transplant was associated with reduced nausea and fatigue seven days after transplant compared with a usual care group; pain, anxiety, and depression were not affected by the intervention.[19] A structured symptom assessment for advanced lung cancer patients,[21] conducted by research nurses and shared with clinic nurses, demonstrated a significant reduction in symptom distress after six sessions over a six-month period when compared with usual care.[21] Finally, a cognitive behavioral intervention reduced symptoms during chemotherapy (CTX) when compared with usual care.[20] Patients with greater symptom severity before treatment, who received the intervention, had lower symptom severity at Weeks 10 and 20 than a usual care control group.

A few psychoeducational intervention studies aimed to reduce fatigue incorporated interventions to manage sleep disturbances. The results have been mixed. Yates et al. demonstrated better fatigue outcomes one week after completion of the intervention; however, the changes were not sustained over the next two cycles of treatment.[22] Ream et al. documented better fatigue outcomes after three cycles of CTX; however, outcomes for the earlier cycles were not reported.[23] Berger et al.[24] evaluated the efficacy of a sleep management intervention to reduce fatigue and improve sleep quality; the intervention group had better sleep quality but not lower fatigue. The results to date do not provide conclusive guidance about the best strategies for management of fatigue and sleep disturbances.

The study reported here extended a beneficial energy conservation and activity management (ECAM) intervention for fatigue to include intervention for sleep disturbance.[3] In addition to the main analysis, the ECAM study showed that, after CTX treatment, 89% of the participants reported fatigue, 71% reported sleep disturbance, 30% reported pain, and 28% reported depression. Sixty-eight percent of those with fatigue also reported sleep disturbance, 30% reported pain, and 28% reported depression. These results provide an indication that other symptoms in addition to fatigue have been problematic during CTX and should be addressed in symptom research.

METHODS

Study Design

The primary aim of this study was to test the efficacy of an EASE intervention during cancer CTX. The primary outcomes were fatigue, sleep disturbance, and functional status. The secondary outcomes were pain and depression. This randomized clinical trial compared the EASE intervention with an intervention controlling for time and attention that consisted of information about nutrition and a healthy diet. The study was conducted at four clinical sites: two university health science centers, a community cancer center, and a comprehensive cancer center. Individuals were eligible if they were 18 years of age or older and were beginning a new CTX regimen with at least one CTX drug administered intravenously in a cyclic manner (on any schedule) for breast, lung, colorectal, prostate, gynecologic, bladder, or testicular cancer or lymphoma. Any prior treatment other than surgery was completed at least one month previously, and the individual could receive concurrent radiation. Participants had to be able to read and write English. Individuals were excluded if their treatment plan included marrow or stem cell transplantation, interleukins, interferons, or tumor necrosis factor; had a chronic fatigue disorder;

were being treated for a diagnosed sleep disorder (such as narcolepsy or sleep apnea); were enrolled in another study that involved a psychoeducational intervention; had a communication impairment; had overt evidence of psychiatric disorder; or initiated treatment for anemia or depression during the previous three weeks.

The Institutional Review Board (IRB) for each study site approved the research protocol in conformity to federal regulations. Potential participants were approached by telephone or in the clinic, and the study was explained. All study participants provided written informed consent. The IRB granted a waiver to retain de-identified demographic information, including age, gender, ethnicity, and race, from individuals who refused to participate in the study for comparison with study participants.

At each of the recruitment sites, breast cancer patients were the largest cancer population, and the group most easily accrued into research because of clinic logistics. Hence, participants in this research were stratified by diagnosis (breast cancer vs. non-breast cancer) at each site to ensure equivalency of the experimental and control groups on this factor. Participants were then randomly assigned to receive either the EASE intervention or the nutrition (control) intervention. Random assignments were generated by the statistician and placed in sealed envelopes that were numbered and selected sequentially for each stratification group.

Procedures

Baseline questionnaires measuring subjective symptoms and functional status were completed on Day 1 of the CTX cycle before receiving treatment and on Day 4 after the first CTX, which coincided with a known time of high fatigue. Also at baseline, an objective measure of sleep disturbance (actigraphy) was obtained along with a companion sleep and symptom diary. Follow-up data points were Days 43–46 or 57–60 depending on the length of the CTX cycle. At both measurement points, patients completed questionnaires and wore the actigraph on the nondominant wrist on Day 1 and removed it 72 hours later (which was Day 4, the equivalent of three 24-hour periods).

Variables

Demographic and clinical information was obtained by a questionnaire (age, gender, race, ethnicity, marital status, education, employment). Clinical data were abstracted from the medical records (diagnosis, stage, comorbidities, previous treatment, and current treatment).

Fatigue was measured with the General Fatigue Scale (GFS), a seven-item Likert-type scale (1 = no fatigue, distress, or impact, to 10 = greatest possible fatigue, distress, or impact).[25] The measure was scored by averaging the responses to the items. Cronbach alpha reliability coefficient for this sample was 0.92.

Fatigue also was measured with the fatigue subscale of the Profile of Mood States (POMS) questionnaire. The POMS was developed to assess transient distinct mood states. Originally designed as a 65-item scale,[26] the current short version consisted of six subscales with a total of 30 items.[27] The fatigue symptom subscale (POMS-F) consisted of five adjectives measuring subjective fatigue (such as weary, tired, and others) that were rated on a 5-point scale, with “0” indicating “not at all” and “4” indicating “extremely.” Items were summed to form a subscale score that ranges from 0 to 20. This scale is well recognized as a sensitive, valid, and reliable measure of the sensation of fatigue, with considerable evidence of validity and reliability.[27,28] The Cronbach alpha coefficient for this sample was 0.94.

To document subjective sleep disturbance, including *insomnia*, the Pittsburgh Sleep Quality Index (PSQI) was used. The PSQI is a subjective, self-rated, paper-and-pencil questionnaire consisting of 19 items. Responses to the 19 items are grouped into seven component scores that are weighted equally on a 0–3 scale. The seven components of the PSQI are sleep quality, latency, duration, habitual efficiency, disturbances, medication use, and daytime dysfunction. The components are summed to produce a global PSQI score that can range from 0 to 21. A higher score indicates more severe complaints and worse sleep quality.[29] Internal consistency reliability and construct validity have been supported in cancer populations.[30,31] In this sample, the Cronbach alpha reliability for the scale was 0.75.

Objective sleep disturbance data also were obtained by means of continuous noninvasive monitoring using wrist actigraphy, an objective record of movement over time in the form of activity counts.[32,33,34] Actigraphy is a valid, reliable measure of sleep that correlates with polysomnography at approximately 90% agreement. It is a sensitive measure of sleep-wake and activity-rest patterns as well as circadian activity rhythms.

The actigraph measure used in this research was the Octagonal Basic Motionlogger® Actigraph from Ambulatory Monitoring, Inc. (Ardsley, NY). It was an unobtrusive instrument resembling a wristwatch that could be worn in the usual environment, both at home and place of employment. Instructions about actigraph use included pushing a small marker on the side 1) when putting on the actigraph for the first time, 2) when turning out the light to go to sleep, and 3) when getting out of bed in the morning. These markers were used to discriminate day from night when performing the analysis.

Several sleep-wake parameters were examined in this research: total time in bed (indicated by the event markers on the actigraph); total sleep time after sleep onset (in minutes); number of awakenings from sleep onset to morning lights on (indicated by an event marker); minutes awake (wake after sleep onset [minutes]); and percent time asleep after sleep onset. Data collected continuously over 72 hours were uploaded to a personal computer using the Micro-Mini® Motionlogger Actigraph Interface Connector and analyzed using the Action 4 analysis program (Copyright© 1988–2001; Ambulatory Monitoring, Inc.). Actigraphy data for up to 72 hours were analyzed in one-minute epochs.

Participants also completed an adapted Morin Sleep Diary to provide confirmation of “lights off” and “lights on” for comparison with the event marker on the actigraph, as well as information about naps, medications, and environmental factors that aid in the interpretation of the actigraph data. The diary has been used in numerous sleep studies[35] in both healthy people and those with cancer.[36,37,38,39] A test of reliability of actigraphy scoring indicated 83.4% agreement between two coders. The intraclass correlation coefficients for each sleep parameter ranged from 0.83 to 0.99.

Pain severity was measured by the intensity subscale of the Brief Pain Inventory (BPI).[40] Patients reported pain severity (worst, least, average, and current pain) using a 0–10 scale for each item (0 = no pain to 10 = pain as bad as you can imagine). The four pain items were averaged to yield a pain intensity score ranging from 0 to 10. The scale is widely used; validity and reliability in cancer treatment have been established. [40], [41] and [42] Cronbach alpha for the BPI intensity scale was 0.88 in this sample.

Depressive symptoms were measured by the depressive symptom subscale of the POMS-D, which consisted of five adjectives describing depression (such as sad, discouraged, gloomy, and others) rated on a 5-point scale, with "0" indicating "not at all" and "4" indicating "extremely." Items were summed to form a score that ranged from 0 to 20. Internal consistency, as measured by Cronbach alpha, was 0.90 in this sample.

Other Side Effects. The side-effect checklist (SCL) is a measure of side-effect severity based on a measure used in our previous research on coping with cancer treatment. Severity of side effects was rated using a 5-point Likert-type scale (0 = not at all severe to 5 = extremely severe). Summed side-effect severity scores have been correlated with outcome measures such as mood and other quality-of-life domains in cancer patients.[43,44] This instrument has acceptable test-retest reliability ($r = 0.84$) and face validity as well as clinical validity.[43,44,45] Cronbach alpha in this study was 0.87.

Functional status was assessed by three measures. Limitation of functioning was measured by adapting the interference items (SXINT) from the BPI[40] to apply to "symptoms" rather than "pain" only. Respondents were asked to describe how symptoms had interfered with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. Each item was rated on a 0–10 scale, with the words "did not interfere" at 0 and "completely interfered" at 10. Internal consistency reliability for this sample was 0.91.

The Short-Form (SF)-12 provided a second measure of functional status. The SF-12 is a shorter version of the 36-item Short-Form Health Survey[46,47] that was developed for the Medical Outcomes Study.[48] The scale includes physical and mental components of quality of life (SF-12-P and SF-12-M, respectively). Items for each component were recoded (as needed), summed, and transformed to a 0–100 scale, with higher scores indicating better physical or mental functioning. The scale is widely used in cancer populations, and norms have been established.[49]

Eastern Cooperative Oncology Group (ECOG) Performance Status is a simple rating of ability to function in usual activities. It has been widely used by clinicians to evaluate participants in drug clinical trials. It has been adapted here for patient self-report.[50] Participants are asked to select from five statements the one that best described their current activity level: 1) I have normal activity without symptoms; 2) I have some symptoms, but I do not need to spend any extra time resting during the day; 3) I need some time to rest (e.g., in bed), but it amounts to less than half of my normal daytime; 4) I need to rest (e.g., in bed) for more than half of my normal daytime; and 5) I am unable to get out of bed. This item was scored on a 0–4 scale.

Interventions

Participants in each intervention group received three telephone sessions with a specially trained oncology nurse. The intervention occurred during the second, third, and fourth week after the first CTX treatment. Written intervention materials included a handbook specific to the EASE or control group. The intervention was delivered using an interactive approach that built on the individual's existing knowledge of energy conservation strategies, sleep management, and his or her unique response to symptoms. A specific protocol and script were used; however, the nurse was trained to customize the protocol to the needs of the participant.

The tenets of the common sense model (CSM)[51,52,53] provided the basis for the EASE intervention. This model is appropriate for the study of multiple symptoms; it proposes three stages of symptom management: representation, coping, and appraisal. In the *representation* stage, the individual gathers information about the symptom's identity, cause, and pattern to form a mental image of the symptom. In the *coping* stage, the individual identifies and implements self-care strategies to manage the symptom. During the *appraisal* stage, the individual evaluates the effectiveness of the strategies and adjusts either the coping methods or symptom representation based on the experience of symptom management.[54]

In this study, a research nurse provided symptom management based on the tenets of the CSM. Information was provided to assist with the formation of an accurate *representation* of the symptoms of fatigue and sleep disturbance. In the first telephone intervention session conducted approximately one week after the first CTX treatment, the research nurse provided information to each participant about the characteristics of the two symptoms; typical causes of each (such as specific drugs, emotional distress, being over- or underactive); and patterns of symptoms (most severe immediately after treatment, tapering off after five to seven days). The nurse engaged the participant in a discussion of his or her experience of fatigue and sleep disturbance, including the likely causes and patterns during the first week after CTX. EASE group participants also received a handbook that included the information about symptoms and examples of energy conservation and sleep management strategies. Between Sessions 1 and 2, participants completed a daily diary (concerning symptoms and sleep patterns) and a priority list of usual activities.

In the second intervention session during the second week after CTX, the nurse used information from the daily diary and priority list to guide the participant to formulate and implement a plan of energy conservation to manage valued activities and a plan for sleep enhancement to manage sleep disturbance (*coping* phase). The plan included suggested strategies to manage each of the symptoms. Energy conservation strategies for fatigue included decision making about delegating activities and responsibilities, pacing oneself, setting priorities, and engaging in demanding activities at times of peak energy. Sleep enhancement strategies included establishing an optimal environment for sleep; learning and using relaxation techniques to induce sleep at the beginning of the night and after nighttime awakenings; restricting sleep to the same number of hours each night and minimizing nap taking; and engaging in regular exercise during daytime hours. The participant was directed to use the plan during the next week. In the third session (*appraisal* stage), the individual evaluated and revised the plan.

The control intervention was designed to control for the amount of time and attention received by the experimental group. The intervention focused on information about nutrition and a healthy diet. This content was chosen, because patients with cancer are interested in this topic and because it is of minor relevance to fatigue during aggressive cancer treatment.[55] Information on maintaining a healthy diet was discussed in the first session, including a description of the food pyramid and healthy food choices. The participant kept a 24-hour dietary record as homework in preparation for the second session. This was discussed during Session 2 for adjustments to their diet if needed, and a discussion about vitamins was carried out. The third session consisted of sharing information about minerals and fiber as well as an evaluation of the helpfulness of the information provided. Therapeutic nutritional information or information on symptom management was not included in the control intervention. The three control sessions were equivalent to the EASE intervention in terms of the amount of time spent with the individual.

The research nurses at Fox Chase Cancer Center conducted all of the interventions by telephone to protect the integrity of the intervention and minimize differences in delivery. Each nurse received eight hours of training in the conduct of the EASE intervention. Training included didactic presentations as well as demonstration and role play. In addition, ongoing bimonthly supervision was provided by one of the investigators. Nurse adherence to the EASE and control interventions was examined using a checklist of the components of each intervention. This checklist was used to evaluate 20% of the audio-recorded interventions (every fifth case) during the first two years of the study to determine adherence to the telephone protocol. Participant use of the EASE strategies was measured with a brief checklist of intervention behaviors. Individual items were summarized as the number of fatigue and sleep management strategies that were used.

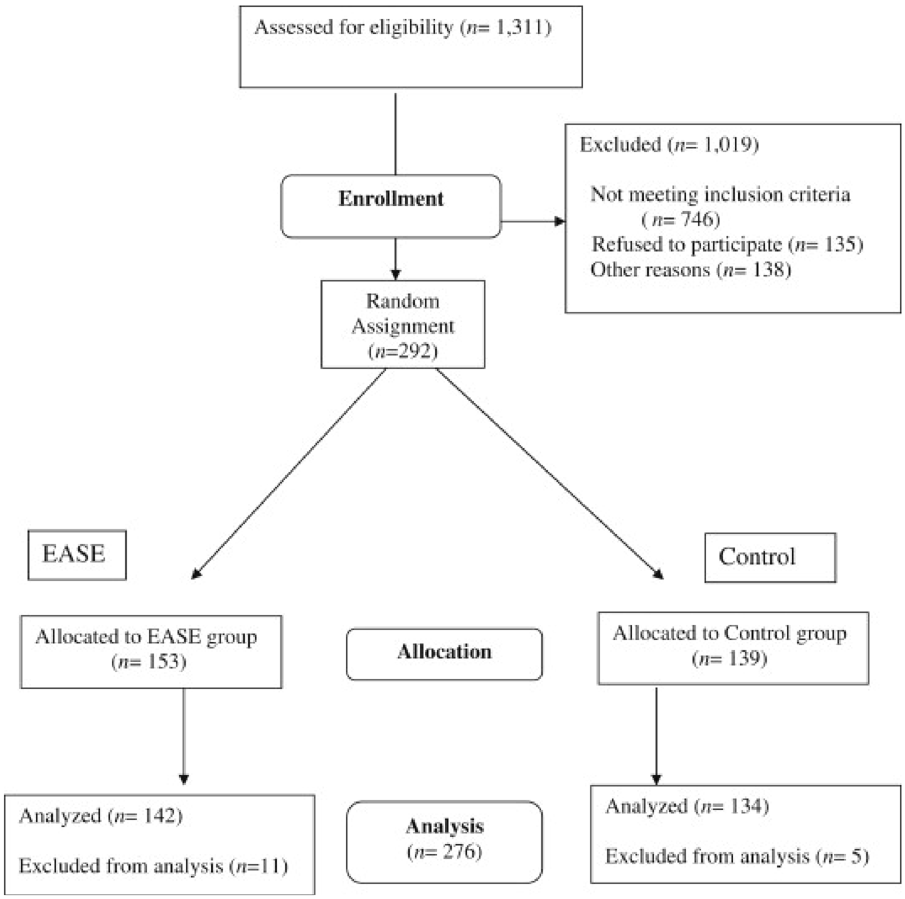
Statistical Analysis

Nonparametric Chi-squared analysis and independent *t*-tests were used, as appropriate, to examine differences between participants and nonparticipants, baseline equivalence between study groups (EASE vs. control), and baseline equivalence between participants who completed all study activities and those who did not. The SAS Mixed Procedure (PROC MIXED; SAS Institute, Cary, NC) restricted maximum likelihood method was used to examine the primary hypothesis,[56] because the study involved repeated measures that were correlated, and there were changes in variability because of attrition. For all analyses, an “intent-to-treat” analysis was conducted, in which all available data for participants were included under the missing-at-random assumption of the mixed-model analysis, and all participants were evaluated as randomized regardless of whether they had completed all three intervention sessions.

RESULTS

One thousand three hundred eleven individuals were assessed for eligibility. Of these, 746 did not meet all inclusion criteria, and an additional 273 declined enrollment (Fig. 1). Common reasons for not enrolling included lack of interest (n = 107), poor timing (n = 28), inability to be contacted (n = 59), and initiation of cancer treatment before consent (n = 33). Two hundred ninety-two individuals were enrolled in the study between February 2, 2004, and August 31, 2007, and were randomized to receive the EASE or control intervention. Sixteen participants were excluded from the analysis, leaving 276 analyzed cases. Reasons for exclusion included severity of illness (n = 4), loss to follow-up (n = 10), and change of treatment (n = 2).

Figure 1: Eligibility, enrollment, and follow-up of study participants.



A comparison between participants and nonparticipants using Chi-squared and *t*-tests showed that participants (n = 276) and nonparticipants (n = 135) differed significantly with regard to age, gender, and cancer diagnosis. Nonparticipants were older and more likely to be males than the participants. Breast cancer, and thus, the number of females, was overrepresented in the participant group, whereas lung cancer was underrepresented.

The final sample (n = 276) was primarily female (83%), Caucasian (90%), married (70%), college educated (42%), and was treated with CTX alone (95%). The most common diagnoses were breast (55%), lung (17%), lymphoma (8%), and ovarian (6%) cancers. The mean age was 53.97 years (standard deviation = 12.02).

Considering the primary outcome variables, patient-reported fatigue (GFS) was moderately elevated at baseline and remained elevated at follow-up in both the EASE and control groups (Table 1a). Similarly, patient-reported sleep disturbance (PSQI) at baseline and follow-up was well greater than the accepted cutoff score of 5 in both groups, indicating moderate levels of sleep disturbance. In contrast to patient-reported perception of disrupted sleep, actigraphy readings indicated that the total sleep time was almost eight hours, and sleep percent was greater than 85% for both groups at both time points, which is in the normal range (Table 1b). Physical functioning (SF-12-P) for EASE and control groups at baseline and follow-up was diminished and similar to the norms for a sample with serious medical illness,[46] as would be expected in this sample of cancer patients undergoing treatment. Mental functioning (SF-12-M) was in normal range for both groups at both time points.

Table 1a: Means and SDs for Patient-Reported Outcomes

	Mean (SD)		
Measure	**Pretreatment Baseline**	**Day 4 Baseline**	**Follow-Up**
Manipulation check			
CLB			
EASE	10.03 (3.78)		13.57 (3.1)
Control	9.5 (3.62)		12.17 (3.09)
Primary patient-reported outcomes			
GFS			
EASE		5.19 (2.14)	4.89 (1.92)
Control		5.12 (2.05)	4.82 (2.03)
POMS-F			
EASE		3.01 (1.13)	2.85 (1.01)
Control		3 (1.03)	2.96 (1.12)
PSQI			
EASE	8.01 (3.96)		7.96 (3.59)
Control	7.83 (4.37)		8.24 (3.83)
SF-12-M			
EASE	48.95 (10.29)		49.56 (9.64)
Control	49.65 (11.11)		49.8 (9.6)
SF-12-P			
EASE	40.3 (11.21)		37.2 (8.97)
Control	41.78 (11.37)		37.95 (9.59)
Secondary patient-reported outcomes			
BPI			
EASE		1.99 (2.16)	2.27 (2.26)
Control		1.7 (2.14)	2.15 (2.25)
POMS-D			
EASE		1.81 (0.94)	1.63 (0.78)
Control		1.95 (0.90)	1.52 (0.66)
SCL			
EASE	0.42 (0.33)		0.65 (0.35)
Control	0.42 (0.34)		0.7 (0.42)
ECOG-PS			
EASE	2.03 (0.96)		2.81 (0.81)
Control	1.91 (0.94)		2.96 (0.72)
SXINT			
EASE	2.5 (2.34)	3.98 (2.56)	3.76 (2.4)
Control	2.5 (2.34)	4.12 (2.57)	3.85 (2.38)

SD = standard deviation; SXINT = symptom interference; CLB = checklist of behaviors; SCL = side-effect checklist.

Because this was a randomized clinical intervention trial, baseline equivalence of the intervention groups was examined for the following clinical and demographic variables: cancer diagnosis, clinical stage, gender, ethnic background, marital status, education, age, and employment status (Table 2). The study groups differed only by employment status—$X^2 = 4.00$, $P = 0.05$. Because employment status could influence the need for and motivation to engage in fatigue reduction and/or sleep disturbance reduction behaviors, it was included as an independent variable in the main analyses.

Table 1b: Means and SDs of Actigraphy Parameters Averaged Over Study Days

	Mean (SD)	
Measure	**Day 1–3 Baseline**	**Follow-Up**
Total time in bed (minutes)		
EASE	543.6 (82.71)	537.82 (93.16)
Control	531.73 (81.42)	519.32 (99.47)
Total sleep time (minutes)		
EASE	465.59 (103.92)	466.53 (118.95)
Control	465.02 (79.11)	461.97 (100.35)
Sleep percent after onset		
EASE	86.52 (11.55)	87.4 (13.08)
Control	88.35 (8.28)	89.48 (8.92)
Awakenings		
EASE	10.47 (5.74)	9.98 (5.46)
Control	9.34 (5.41)	8.17 (5.01)
Wake after sleep onset (minutes)		
EASE	69.1 (53.85)	63.63 (63.56)
Control	61.3 (44.87)	53.6 (47.09)

SD = standard deviation.

Of the 276 participants, 60 had some missing data. Baseline equivalence between complete and incomplete cases on overall symptom burden (SCL), fatigue (GFS), and functional status (SF-12, symptom interference) was conducted using independent-samples *t*-test. Results show that the incomplete cases had worse health at baseline before treatment than those who completed the study: SCL ($t(270) = 3.212$, $P = 0.001$ [two-tailed]), SF-12 physical ($t(271) = 2.346$, $P = 0.02$ [two-tailed]), SF-12 mental ($t(83.70) = 2.034$, $P = 0.045$ [two-tailed]), and symptom interference ($t(83.93) = 2.756$, $P = 0.007$ [two-tailed]). Complete and incomplete cases did not differ on fatigue or sleep disturbance measures. Chi-squared analysis showed no difference in the number of complete cases between the two intervention groups—$X^2 = 0.551$, $P = 0.458$. These findings suggest that, in both groups, participants who were in poorer health at baseline were more likely to have incomplete data.

One hundred fifty-three participants were allocated to the EASE group and 139 to the control group (Fig. 1). Seventy-five percent of the EASE participants and 83% of the control group received all three sessions of the intervention. The total amount of intervention time for each group was similar (EASE = 69 minutes; control = 72 minutes). A manipulation check was conducted to determine whether the EASE and control groups differed in the use of intervention strategies. At baseline and follow-up, participants in both study groups completed a behavioral checklist; 10 items referred to energy conservation strategies (delegation, planning, pacing, and others), and nine items described sleep promotion strategies (using relaxation strategies, avoiding caffeine before bedtime, establishing set sleep-and-wake times, others). A repeated measures analysis of variance (ANOVA) revealed that the EASE group used significantly more intervention strategies over time compared with the control group (Table 3a). This finding indicates that the EASE intervention influenced participants as predicted: individuals who were taught behavioral strategies to manage fatigue and sleep disturbance reported using more than did the control group who were not taught these strategies.

Table 2: Differences in Demographic and Clinical Characteristics of Study Groups[a]

Characteristic	EASE Group *n* (%)	Control Group *n* (%)	*P*-value
Age (years) (*n* = 276)			0.42
Mean (SD)	54.4 (11.8)	53.5 (12.3)	
Gender (*n* = 276)			0.29
Female	114 (80.3)	114 (85.1)	
Male	28 (19.7)	20 (14.9)	
Ethnicity (*n* = 264)			0.66
Non-Hispanic	132 (96.4)	121 (95.3)	
Hispanic	5 (3.6)	6 (4.7)	
Race (*n* = 272)			0.47
American Indian/Alaska Native	3 (2.1)	1 (0.8)	
Asian	1 (0.7)	2 (1.5)	
Black or African American	7 (5.0)	11 (8.3)	
White or Caucasian	127 (90.7)	115 (87.1)	
More than 1 race	1 (0.7)	3 (2.3)	
Unknown	1 (0.7)	0 (0)	
Marital status (*n* = 272)			0.39
Single	9 (6.4)	13 (9.8)	
Separated or divorced	24 (17.1)	17 (12.9)	
Widowed	7 (5.0)	11 (8.3)	
Married	100 (71.4)	91 (68.9)	
Education (*n* = 271)			0.38
8th Grade or less	1 (0.1)	3 (2.3)	
Some high school	3 (2.1)	8 (6.1)	
High school graduate or GED	31 (22.1)	24 (18.3)	
Technical school graduate	6 (4.3)	8 (6.1)	
Some college	41 (29.3)	32 (24.4)	
College graduate	58 (41.4)	56 (42.7)	
Currently employed (*n* = 272)			0.05[a]
Yes	69 (49.3)	81 (61.4)	
No	71 (50.7)	51 (38.6)	
Study site (*n* = 276)			0.79
Fox Chase Cancer Center	75 (52.8)	77 (57.5)	
University of Utah	47 (33.1)	41 (30.6)	
University of Cincinnati	15 (10.6)	11 (8.2)	
Christiana Medical Center	5 (3.5)	5 (3.7)	
Diagnosis (*n* = 276)			0.2
Breast	73 (51.4)	79 (59.0)	
Lung	21 (14.8)	26 (19.4)	
Colorectal	8 (5.6)	5 (3.7)	
Prostate	2 (1.4)	1 (0.1)	
Gynecologic	19 (13.4)	13 (9.7)	
Testicular	0 (0)	1 (0.1)	
Lymphoma	14 (9.9)	9 (6.7)	
Bladder	5 (3.5)	0 (0)	
Known clinical stage (*n* = 246)			0.65
1	25 (19.7)	19 (16.0)	
2	47 (37.0)	43 (36.1)	
3	31 (24.4)	37 (31.1)	
4	24 (18.9)	20 (16.8)	

[a]Sample size varied by reporting of specific information.

A repeated measures ANOVA was used to test the efficacy of the EASE intervention. Three hypotheses were tested. Compared with the control group, it was predicted that the EASE intervention group would report: 1) less fatigue over time, 2) less sleep disturbance over time, and 3) less disruption of functional status over time. Each measure of the primary outcomes (fatigue, sleep disturbance, and functional status) was examined in a separate repeated-measures ANOVA (Table 3a). Actigraphy measures of sleep were analyzed in a similar manner (Table 3b). In each analysis, there was a single between-subject independent variable—study group with two levels (EASE or control). In addition, there was a single within-subject variable—time (with two occasions of measurement). Current employment was included in the analysis as an additional independent variable, because the intervention and control groups differed on this variable. The EASE and control groups did not differ on fatigue (GFS and POMS-F), sleep disturbance (PSQI and actigraph measures), or functional status (SF-12-M or SF-12-P) over time. There were significant three-way interactions for symptom interference (SXINT), pain (BPI), and depression (POMS-D), indicating that unemployed individuals who received the EASE intervention had less pain and less interference with functioning than employed individuals in the same group. Although these differences were statistically significant, the actual differences were small and, therefore, not clinically meaningful.

Table 3a: F-Test (Repeated-Measures Design with Maximum Likelihood Estimates) and P-Values for Patient-Reported Outcomes

Measure	df	Study Group	Time	Working Status	Study Group by Time	Study Group by Working Status	Study Group by Time by Working Status
Manipulation check							
CLB	1/268	6.38[a]	163.38[b]	0.00	4.91[a]	0.00	0.14
Primary patient-reported outcomes							
GFS	1/262	0.22	2.91	0.13	0.02	0.06	0.81
POMS-F	1/250	0.26	0.95	0.56	0.47	1.29	0.11
PSQI	1/265	0.05	0.11	0.30	0.58	0.17	0.00
SF-12-M	1/268	0.62	0.00	0.24	0.00	0.49	1.94
SF-12-P	1/268	0.84	28.42[b]	0.18	0.18	0.70	0.74
Secondary patient-reported outcomes							
SXINT (T1a-T1b-T2)	2/268	0.01	46.20[b]	0.64	0.37	0.00	3.64[a]
SXINT (T1a-T2)	1/268	0.00	46.29[b]	1.80	0.86	0.53	6.87[c]
SXINT (T1b-T2)	1/260	0.11	0.84	0.63	0.01	0.44	5.17[a]
BPI	1/261	0.94	4.44[a]	0.65	0.32	0.09	3.95[a]
SCL	1/268	0.29	106.59[b]	1.85	0.00	0.29	0.00
POMS-D	1/184	0.00	16.94[b]	0.31	1.94	0.01	6.85[c]
ECOG	1/263	0.42	150.82[b]	4.93[a]	3.26	3.35	0.07

SXINT = symptom interference (T1a = Time 1a; T1b = Time 1b); CLB = Checklist of Behaviors; SCL = side-effect checklist.
[a]$P < 0.05$. [b]$P < 0.001$.[c]$P < 0.01$.

Because of the overall null result of the study, we conducted a post hoc subset analysis to determine if other factors could have influenced the study results. In separate analyses, gender, cancer diagnosis (breast cancer vs. non-breast cancer and lung cancer vs. non-lung cancer), and baseline ECOG performance status were added to the linear mixed method analysis as independent variables. These analyses (study group-by-covariate-by-time interaction) were used to examine whether the intervention benefited a specific group (such as males or females, breast or other cancers, and others). Although several of these factors were associated with the primary outcomes, there were no significant interactions between these factors and study group assignment.

Table 3b: F-Test (Repeated-Measures Design with Maximum Likelihood Estimates) and P-Values for Patient-Reported Outcomes

Measure	df	Study Group	Time	Working Status	Study Group by Time	Study Group by Working Status	Study Group by Time by Working Status
Total time in bed (minutes)	1/251	1.21	0.55	0.64	0.32	0.13	0.31
Total sleep time (minutes)	1/251	0.00	0.22	1.38	0.17	0.96	0.09
Sleep percent after onset	1/251	1.71	3.52	8.47[b]	0.07	0.80	0.04
Number of awakenings	1/251	2.78	4.99[a]	0.33	1.39	0.17	1.46
Wake after sleep onset (minutes)	1/251	1.50	4.76[a]	8.12[b]	0.12	0.80	0.05

[a]$P < .05$. [b]$P < .01$.

DISCUSSION

The study results indicate that the EASE intervention did not improve fatigue, reduce sleep disturbance, or prevent functional decline during CTX. Both intervention and control groups demonstrated an increase in fatigue and decline in physical functioning. There was no difference over time between the intervention and control groups despite the fact that the EASE intervention group reported using more behavioral intervention strategies that had been taught than the control group. A positive outcome in both groups was a decrease in the average number of nighttime awakenings over time. The finding that unemployed individuals benefited more from the EASE intervention than those who were employed raises questions about the burden associated with behavioral interventions for individuals who continue to work during cancer treatment.

The results are puzzling, because a previous intervention trial[3] of fatigue management using the energy conservation (ECAM) component of the current intervention demonstrated a modest reduction of fatigue during treatment. This follow-up study built upon that successful intervention by introducing an additional intervention component that was proposed to have a more powerful beneficial effect on fatigue, sleep disturbance, and functional status than was previously observed.

To make sense of the study results, we have considered several potential explanations. The first possibility is that differences in the design of the two studies could have influenced the outcome. In fact, there were four important differences between the two studies: type of cancer treatment, complexity of CTX regimens, amount of intervention provided, and timing of the outcome measures.

In the previous ECAM clinical trial, 47% of the sample received CTX, 44% had radiotherapy, and 9% got both treatment modalities concurrently. The two groups that received CTX had more severe fatigue and worse functional status over time than the radiotherapy group. It is possible that the radiotherapy group benefited more from the ECAM intervention and contributed more to the improvement of fatigue scores than the CTX groups. Despite the EASE intervention, a significant increase in fatigue and sleep disturbance and a decline in functional status occurred from before to after CTX. It is possible that the intervention was not powerful enough to overcome the negative effect of CTX on symptoms and functioning.

Another difference between the two studies is that the number and complexity of CTX regimens has changed dramatically over the years. In the previous study, most cytotoxic CTX was given on a 21- or 28-day schedule, with drugs given on the first day by bolus or infusion followed by a three- or four-week recovery period. In the EASE study, CTX regimens were more variable, intensive, and complex. The oxaliplatin and infusional 5-fluorouracil (FOLFOX) regimen for colorectal cancer involved a 48-hour infusion every 14 days; sometimes, the biologic, bevacizumab, also was given. Dose-dense CTX for breast cancer consisted of four 14-day cycles of doxorubicin and cyclophosphamide followed by four 14-day cycles of paclitaxel; in some cases, trastuzumab was given with paclitaxel. For participants who received this regimen, the final data collection point coincided with the first cycle of paclitaxel. Some CTX regimens for lung cancer were given weekly; others were given every week for three weeks followed by one week of recovery. All of these treatment variations could have increased the intensity of treatment-related symptoms such that an intervention focused on only two symptoms was no longer powerful enough to be effective. In fact, our measure of other treatment side effects demonstrated a dramatic increase in the intensity of symptoms over time and wider variability in the number and intensity of symptoms reported by study participants. It is also possible that the variability of CTX regimens resulted in different patterns of fatigue and sleep disturbance for each regimen.

A third difference between the two studies was the amount of behavioral intervention provided. In both trials, the intervention was conducted by telephone in three separate sessions. The previous intervention was focused on providing information about fatigue and teaching energy conservation skills. In the current trial, information was provided about both fatigue and sleep disturbance; both energy conservation and sleep modification strategies were taught. It is possible that the amount of time spent in the intervention (intervention dose) for the EASE condition was insufficient for individuals to develop skill in using both energy conservation and sleep improvement strategies as well as to incorporate these strategies into their daily lives.

Another potential explanation for the lack of intervention effectiveness could be the number of intervention sessions received by participants (dose). Only three intervention sessions were conducted in contrast to other intervention trials for multiple symptoms. [19], [20] and [21] In those studies, more sessions appeared to equate with more consistent benefit from the intervention. A meta-analysis has also suggested that 8–10 sessions of psychoeducational intervention are needed to achieve maximal behavior change.[57]

A fourth difference in the two studies was the timing of the outcome measures. In the previous ECAM trial, measurements were taken before the first CTX cycle and three days after the second and third CTX treatments. Fatigue scores measured before the initiation of CTX were lower than the two measurements taken after the next two CTX sessions. Reasoning that fatigue and sleep disturbance could be elevated before and after CTX, baseline measures of the primary outcomes in the current study occurred before treatment and four days after CTX treatment. Then, changes in the primary outcomes (if present) would be more clearly attributed to the EASE intervention. Despite the improved study design, we did not observe the expected decrease in fatigue and sleep disturbance or improvement of functional status for the EASE group, indicating that the intervention did not have the predicted effect. Given the complexity and variability of the CTX regimens in this study, it is possible that the timing of our measures did not capture symptom changes because of the intervention, because individuals receiving weekly or biweekly therapy may have an up-and-down pattern of symptoms corresponding to each dose of CTX.[58]

Another potential explanation for the result is the possibility that a large number of participants had low fatigue and/or sleep disturbance or symptoms that were not severe enough to demonstrate improvement because of the EASE intervention. Three days after the first CTX treatment, 29% of the EASE sample reported fatigue scores less than 4 on a 1–10 scale, indicating that almost one-third of study participants had a low level of fatigue. Likewise, 50% of participants rated their usual sleep quality as “fairly good” or “very good” before intervention; also, actigraph results demonstrated that two-thirds of the sample had sleep efficiency ratings (the ratio of time asleep and total time in bed) of 85% or greater three days after CTX, which is considered normal. This suggests the presence of a “floor” effect that could have influenced study results; it also argues against the assumption that everyone who gets CTX will have a high level of fatigue or sleep disturbance requiring intervention.

Future Directions

Several lessons learned form the basis for recommendations for future symptom management studies. We noted that the timing of measures was not optimal in the context of the complex treatment regimens that were used in the EASE study. There are at least two ways to approach this problem. First, it may be possible to limit variability by limiting study eligibility to a few diagnoses and treatment regimens. However, this may still leave considerable variability. Using the example of breast cancer treatment, one study noted 16 regimens, at least four of which were commonly used.[24] It is also likely that new regimens will continue to be introduced during the course of a symptom management trial. A second approach would be more frequent monitoring of symptoms. However, this approach also has deficiencies with regard to patient burden and adherence. It is critical to identify efficient and simple methods for symptom monitoring, such as automated systems.[59,60,61,62,63]

Another issue that needs exploration is the amount or “dose” of symptom intervention. Intervention efficacy could be related to the dose of intervention (number and frequency of intervention sessions); yet, little is known about the dose of intervention needed to alleviate multiple symptoms. Although most behavioral intervention studies have described the “intended” time or amount of intervention, few studies have examined the “actual” amount of intervention delivered. It is not clear whether an optimal dose of intervention is a fixed amount or a variable dose that is adapted to symptom severity. Future intervention trials would benefit from an exploration and by possibly tailoring the intervention dose. In addition, trials involving a tailored intervention targeting symptoms as part of a symptom cluster would be beneficial.

Attention also must be paid to symptom severity as a potential eligibility criterion for symptom management trials. A run-in period could be used to monitor symptoms so that a minimum level of symptom severity can be documented for eligibility to participate. Finally, it may be necessary to compare a symptom intervention with a usual-care control group.

Despite the lack of positive findings from this clinical trial, it is essential to continue to examine behavioral interventions for symptom management during CTX. There are several reasons for this recommendation. First, many individuals with multiple symptoms during CTX could benefit from effective behavioral interventions. “Behavioral” interventions are identified, because symptom management focuses primarily on patient behavior. Although medication may be prescribed for a symptom, symptom management focuses on the use of drugs and behavioral strategies for optimal benefit. Second, the results of previous research suggest that benefit can be derived from symptom management conducted over time by skilled nurses. [19], [20] and [21] Further research could inform nurses of the most effective management methods to control symptoms.

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