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Testing the Differential Effects of Symptom Management Interventions in Cancer

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ABSTRACT

Objective: The purpose of this study was to test for moderating effects of patient characteristics on self-management interventions developed to address symptoms during cancer treatment. Patient's age, education and depressive symptomatology were considered as potential moderators.

Methods: A secondary analysis of data of 782 patients from two randomized clinical trials was performed. Both trials enrolled patients with solid tumors undergoing chemotherapy. After completing baseline interviews, patients were randomized to a nurse-delivered intervention versus intervention delivered by a "coach" in trial I, and to a nurse-delivered intervention versus an intervention delivered by an automated voice response system in trial II. In each of the two trials, following a 6-contact 8-week intervention, patients were interviewed at week 10 to assess the primary outcome of symptom severity.

Results: While nurse-delivered intervention proved no better than the "coach" or automated system in lowering symptom severity, important differences in the intervention by age were found in both trials. Patients $\leq$45 years responded better to the "coach" or automated system; while those $\geq$75 years favored the nurse. Education and depressive symptomatology did not modify the intervention effects in either of the two trials. Depressive symptomatology had a significant main effect on symptom severity at week 10 in both trials ($p=.03$ and $p<.01$, respectively). Education was not associated with symptom severity over and above age and depressive symptomatology.

Conclusions: Clinicians need to carefully consider the age of the population when using or testing interventions to manage symptoms among cancer patients.

INTRODUCTION

Targeting interventions to characteristics of specific groups of patients has been supported in research studies and frequently discussed as desirable. While a positive finding of efficacy or effectiveness of an intervention provides evidence base for clinical practice, a negative finding could result from differing effects of the intervention on subgroups of the population. Thus, in addition to the overall comparison of an intervention to usual care or another intervention, it is important to test for moderating effects to identify potential efficacy for subgroups of the population [1]. The examination of moderating effects of patient characteristics on intervention efficacy is fraught with difficulty [2,3]. Post hoc tests for characteristics, such as age, may lack discrimination because distributions are skewed toward older ages. This is especially true in those with cancer, as the majority is diagnosed at an older age [4,5]. Further, by design, most trials are powered to detect main effects but underpowered to detect the differential effects of the intervention by patient characteristics. Even when moderating effects are observed, it is unlikely that similarly constructed samples are available for replication. Thus, moderating effects are seldom tested, and as a result, are not incorporated into the inclusion criteria or used as stratification or minimization variables in randomized trials [3].

This paper focuses on two large trials of self-care interventions aiming to manage cancer patients' symptoms during chemotherapy. The purpose of this work was to test for the moderating effects of patients' characteristics in each trial and then to compare the findings from the two trials. The similarity between the two trials provided a unique opportunity to determine whether moderating effects can be replicated.

The nurse-delivered symptom management intervention common to the two trials was developed based on the principles of cognitive behavioral therapy [6,7]. Nurses helped patients

isolate symptom-related problems and taught patients how to assume control for solving these problems and how to use symptom management strategies so that they fit in patient's daily lives [8]. The nurse-delivered intervention, which included both cognitive-behavioral and educational elements, was compared to the educational interventions in both trials. The education intervention implemented as the second arm in each of the two trials involved referral of the patients to a written guide that contained information on symptom management strategies. In Trial I, this educational intervention was delivered by a non-nurse "coach," and in Trial II, the educational intervention was delivered by an automated telephone system. The two trials enrolled similar samples of patients and incorporated the same self-management intervention delivered by a nurse in one of the arms, and the same educational intervention in the other arm (with different modes of delivery in two trials). Patient characteristics tested as potential moderators were selected based on the literature reviewed below and included age, education, and depressive symptomatology.

With few exceptions [9-12], findings indicate that interventions that incorporate cognitive behavioral approaches are equal to, or in some cases, superior to other psychological interventions [13-16]. Combinations of cognitive behavioral and educational strategies have demonstrated effectiveness at reducing symptom severity from side effects of cancer treatment [17,18].

The literature on moderating effects for symptom management interventions in chronic diseases including cancer has mixed findings. A meta-analysis of insomnia trials indicated that adults who were 55 years of age and older responded to cognitive behavioral strategies more favorably in terms of sleep efficiency and total sleep time when compared to adults less than 55 years of age [19]. Conversely, a study examining cognitive behavioral intervention for symptom

management of patients with advanced cancer found older age reduced the effectiveness of the intervention [17] Another study found that age did not modify the effect of the behavioral intervention on symptom severity [12]. Evaluations of possible moderating effects of education are limited. Education moderated individuals' responses to attitude measurement [20,21]; and influenced women's responses to genetic counseling and testing for breast/ovarian cancer [22].

Depressive symptoms in cancer patients are widely studied across numerous primary and specialty care settings [23]. For most cancer patients these symptoms are not sufficiently severe to warrant a full clinical diagnosis of depression [24,25]. Research with cancer patients who do not meet the criteria for a clear diagnosis of clinical depression are summarized as depressive symptoms. Data from several meta-analyses, and our own past trials, suggests that cognitive behavioral and educational strategies can influence cancer- and treatment-related symptoms as well as depressive symptoms [26-30]. There is strong evidence that chronic diseases increase patient depressive symptoms, but few investigations exist about the possible moderating effects of depressive symptomatology on cancer patients' responses to interventions for symptom management [31]. A Cochrane review [32] and a meta-analysis of 6 trials [33] demonstrate the effectiveness of both cognitive behavioral and educational interventions on depressive affect in patients with cancer, suggesting possible mediation but not necessarily moderating effects of depressive affect in symptom management in cancer.

In summary, interventions that incorporate cognitive behavioral and/or educational strategies can assist patients with different chronic diseases to manage their symptoms. Some evidence indicates that age, education, and depressive affect may moderate the impact of these interventions on symptom severity; however, none of the existing studies have attempted to replicate moderating effects of these patient characteristics across similarly designed trials. This

report fills this gap by presenting the secondary analyses of each of the two completed and similarly designed symptom management trials. The research question of moderating effects of age, education, and depressive symptomatology is answered for each trial, and the findings are compared to assess their replication from one trial to the other.

METHODS

Below we describe the two trials and summarize the published findings that were based on the analyses of additive effects of trial arms following the intent to treat principles [17,18].

Setting and Sample

Enrollment for the original trials occurred at two comprehensive cancer centers, two community cancer oncology programs, and five hospital affiliated community oncology centers. Institutional review board approvals were obtained from each site. Registered nurses from these sites implemented the recruitment protocol. To be eligible for either trial, patients met the following inclusion criteria: 21 years of age or older, a diagnosis of a solid tumor or non-Hodgkin's lymphoma, undergoing intravenous chemotherapy, able to speak and read English, having a touchtone phone, and without hearing deficits. Based on our prior results, following consent and prior to enrollment, each trial used a specific symptom severity criteria that used a scale ranging from 0 (no symptom) to 10 (worst possible) [18]. Patients scoring a severity of two on pain and fatigue or a three on pain or fatigue and who had a family caregiver entered Trial I. Patients scoring a two or higher on any symptom entered Trial II. All but 2 patients who completed screening entered either Trial I or Trial II [34]. The two patients who never reached a two in severity on any symptom were sent a letter thanking them for their participation and no further interviews were conducted. Figure 1 summarizes the flow of patients in both trials.

Trial Arms

All arms of the trials were delivered entirely by phone with nurse-delivered symptom management intervention implemented as an arm in each trial. In Trial I, a 6-contact 8-week nurse-delivered self-management intervention was compared with a 6-contact 8-week educational intervention delivered by a non-nurse "coach." In Trial II, a 6-contact 8-week nurse delivered self-management intervention was compared with a 6-contact 8-week automated voice response (AVR) system. During each of 8 telephone contacts spread over 10 weeks (conducted by nurse, "coach," or AVR, respectively), the severity of 16 symptoms (fatigue, pain, dyspnea, insomnia, anxiety, depression, nausea/vomiting, difficulty remembering, dry mouth, poor appetite , numbness and tingling, diarrhea, cough, constipation, weakness, and alopecia) was rated by patients using the scale from 0 (no symptom) to 10 (worst possible). If a patient rated any symptom at a severity of 4 or higher (threshold) at any contact, they received management strategies [35].

For symptoms at 4 or higher, the "coach" in Trial I and the AVR in Trial II referred the patient to a section of a written Symptom Management Toolkit (SMT), which has been proven effective in several trials [8,18,36] to assist in managing the symptoms. This printed SMT, which was developed and refined through previous studies, was written at the 6^{th} grade level and contained evidence-based self-care strategies specific to each symptom [31,37]. Each symptom was presented in an identical format of frequently asked questions: what the symptom is, how people describe it, the causes of the symptom including medications, and a set of strategies presented in short points for managing the symptom. At contacts 2-6, the "coach" or the AVR asked the patient if they read the section of the SMT, and if so, how successful it was for

managing symptoms reported at the last contact. Patients who did not read assigned sections of the SMT, or who rated it unsuccessful, were encouraged to read the section again and continue to

follow the strategies. Thus, the content of the educational interventions delivered by the "coach" and AVR was identical, only mode of delivery differed. In contrast to these two targeted approaches of referral to the SMT, the nurse arms of the trials offered more specific approaches to symptom management based on patients' responses, in addition to the referral to SMT. Nurses worked in partnership with the patients on prioritizing which symptoms experienced by patients should be addressed. Then, nurses used a drop-down list of strategies (specific and relevant to each symptom) on their computer screen to select strategies for the management of selected symptoms. The list of strategies that could be delivered by nurses was broader than the list in the SMT and could include nurses' clinical judgment. Symptom management strategies delivered by nurses were organized into four domains: teaching (adherence to medications, prioritizing, limiting daily tasks), prescribing (diet, exercise, lifestyle changes), counseling and support (coping strategies, reframing), and communicating with healthcare providers (how to report problems, prepare for appointments, ask for help). According to the nurse intervention protocol, up to four strategies could be delivered for each symptom at each phone contact. At contacts 2-6, nurses asked patients if they had tried the previously suggested interventions, and if so, how successful it was for managing the symptom. Interventions not tried or unsuccessful were replaced with new ones, and a suggestion was made to continue the successful interventions.

Measures

Age, sex (male or female), site of cancer (breast, prostate, lung, colon, or Hodgkin's Lymphoma), stage of cancer (I—IV) and comorbidities were obtained from the patients' medical

records. Based on the distribution of age and its non-linear relationship with symptom severity, age was grouped into five categories: 45 years or younger, 46 to 55 years, 56 to 65 years, 66 to 75 years, and older than 75 years of age. Patients' educational levels were collapsed into three categories: high school or less, more than high school to completed college, and graduate or professional education. The Center for Epidemiological Studies- Depression [38], a 20 item reliable valid instrument with responses assessed on four-point scale (0-3), a range of 0 to 60, was used to assess depressive symptomatology during intake. Although not designed for clinical diagnosis due to relatively low specificity, the score of 16 is an established highly sensitive screening cut-off for clinical depression [38,39], and for analysis, the CESD variable was dichotomized as less than 16 versus 16 or higher. The *Symptom Experience Inventory,* developed in past studies by Given et al. [35,40,41] (internal consistency reliability of .79), was used to assess symptom severity during screening, baseline interview, the six intervention contacts, and 10 week interview. The severity of each symptom was rated from 0 (no symptom) to 10 (worst possible), and severity scores were summed across the 16 symptoms to create an index of severity ranging from 0 to 160 [17]. The symptom list from the interviews differed slightly from the list from the six intervention contacts. During the interviews, nausea and vomiting were separated into 2 items, and a single item of depression asked during the intervention contacts was replaced with the CESD for a more detailed assessment of depressive symptoms.

Previous results from the two trials

In both trials I and II, no differences in summed symptom severity were found between the trial arms in the intent-to-treat analyses [18,42]. All four intervention arms had significant improvements in symptom severity over baseline [43]. Per protocol analyses revealed differences in patient subgroups and success with the management of specific symptoms. First,

nurses were more successful than the AVR in retaining lung cancer patients and managing their symptoms [18]. When compared with patients in the nurse arm of Trial II, patients in the AVR arm had a better response to the management of anxiety, depression, poor appetite, cough and fatigue. In Trial II, nurses were more successful than the AVR in managing cancer pain [36]. These findings are from intent-to-treat and per protocol analyses that included the main effect of trial arm variable within each trial, but no interaction terms. This paper extends the completed primary analyses to include tests of moderating effects of the patient characteristics based on the significance of the interactions of trial arm variable with patient characteristics. While both trials were powered to detect main effects of the moderate size, neither trial was formally powered to detect these interactions. We draw upon the similarity of the design of the two trials to assess if any evidence of moderating effects in one trial is replicated in the other one.

Data Analyses

Since separate randomization procedures were carried out for each trial, the analyses of data from each trial were performed separately and the results compared. Descriptive statistics for the demographic, outcome and potential moderator variables were obtained. The baseline differences between the groups in each of the trials were evaluated using chi-square and t-tests. Attrition analyses were conducted to examine the baseline characteristics of patients who dropped out between baseline and week 10 and were compared by trial arm according to the potential moderators.

To determine if age, education, or depressive affect moderated the impact of the interventions on symptom severity, the criteria established by Baron and Kenny [2] and Kraemer et al. [3] were followed. Age, education, and depressive symptomatology were evaluated at baseline to determine if they had a main effect on symptom severity at week 10 and if there was

a significant interaction between each potential moderator variable and intervention arm variable. Least squares (LS) means, also known as adjusted means of symptom severity, were calculated according to the interaction terms. Further, the moderating effect of age in both trials was tested in the presence of depressive symptoms and education variables as main effects and in the interaction with intervention arm to evaluate if the effect of age persisted after adjusting for the level of education and depressive symptomatology. P-values in tables are reported without adjustments for multiple comparisons. When LS means for multiple age groups were compared by intervention arm, conclusions about significance were made using Bonferroni correction. For example, when five age groups were tested, a significance was indicated by $p<.01$ instead of $p<.05$ to control the overall probability of type I error. All analyses were performed using SAS version 9.3.

RESULTS

Table 1 summarizes the socio-demographic information, sites and stages of cancer for each arm of the two trials. Table 2 provides the means and standard deviations of symptom severity and CESD scores at intake. Baseline equivalence was achieved between the arms for the two trials. When baseline scores were compared for cases lost versus those retained at week 10 with respect to age, education, depressive symptomatology, and symptom severity, no differences were found between arms within trials. Thus, any moderating effects are unlikely to be confounded by differential attrition between arms. Figure 1 displays the flow of patients through the two trials. At intake, all patients were undergoing chemotherapy, as this was one of the inclusion criteria. At week 10, in trial I, 51% of the patients in the nurse arm and 58% in the "coach" arm remained in treatment ($p=.38$ for arm difference). The corresponding figures for

trial II were 58% for the nurse arm and 59% for AVR (p=.88). Thus, symptom severity at week 10 did not differ by treatment status (ongoing versus completed or stopped) in either trial. After adjusting for symptom severity at baseline for each trial, there was no significant difference for symptom severity at week 10 and there were no main effects for age or education in either trial. Depressive symptoms at baseline were significantly associated with symptom severity at week 10 in both trials (p=.03 and p<.01, respectively, see Table 3). When testing for moderating effects, age by group interactions were not significant for trial I but were significant for trial II (see Table 3), due to the smaller sample size of trial I.

Examining the adjusted means for symptom severity by age at week 10 revealed a remarkably similar pattern with the differences in the age categories for the trials (see Table 4). Among patients 45 years of age or younger, the self-care strategies delivered by the AVR were more successful than the intervention delivered by the nurse in lowering symptom severity at the 10 week assessment (p<.01). The comparison of the "coach" versus nurse arm in Trial I showed a similar relationship between LS means, but the difference did not reach statistical significance. LS means of symptom severity in trial I were 29.28 for the nurse arm and 19.16 for the "coach" arm, and in trial II, 30.39 for the nurse arm and 15.63 for the AVR arm at week 10. The pattern of LS means reverses for patients 75 and older compared to younger patients in both trials. In trial I, the LS means of symptom severity at week 10 were 18.04 for the nurse arm and 34.67 for the "coach" arm, and in trial II, 19.84 for the nurse arm and 26.35 for the AVR arm. Even though the magnitude of the differences between LS means by arm were similar for the two trials, the differences in sample sizes (see Table 1) resulted in the LS means being statistically significant for trial II but not trial I. In the middle-aged categories, 46-55, 55-65, and 66-75, both arms in each trial appear to be equally successful.

Tests for the moderating effects of education and depressive symptoms by arm revealed no associations with symptom severity at the 10-week end point. Education had neither a main nor moderating effect, and depressive symptoms had a main effect on symptom severity at week 10 but did not moderate the effects of the interventions. The LS means by age and arm listed in Table 3 did not change after adjusting for education and depressive symptoms and are not presented. Thus, the moderating effect of age on patient response to the trial arms is not influenced by education or depressive symptoms, and the observed effects for age are not artifacts of educational attainment.

DISCUSSION

Findings from these two trials contribute important information about differential effects of the interventions and the need to select the best performing interventions for specific patient subgroups. A carefully constructed intervention delivered by specially trained nurses was compared against an interpersonal "coach" and an AVR with referral to a SMT. When data from all patients were analyzed according to the intent-to-treat principle, an elaborate nurse-delivered symptom management intervention fared no better than streamlined approaches, where patients were directed to follow specific written directions on their symptoms that were assessed above a severity threshold. When several patient characteristics were examined in relation to the intervention effect, only age showed evidence of modifying the effects of interventions. In the assessment of moderating effects of age, several limitations deserve notice. First, in both trials the numbers of patients in the youngest and oldest age groups were relatively small. Second, we obtained these findings using age as a categorical variable. After evaluating alternatives, we used categories that best fit the data because the effect of age was non-linear. Finally, our sample had

a large proportion of women and relatively low proportion of minorities, reflective of the population of patients treated at the participating oncology clinics. Despite these limitations, the core strength of our argument regarding the moderating effects of age relies on the fact that the patterns of differences according to age were the same across separate but very similarly constructed trials, each designed to address a common endpoint.

The nurse-delivered intervention required an average of 54 minutes per contact while the AVR required only 20 minutes, and the associated costs per contact were around $60 for the nurse arm and $17 for the AVR arm [43]. However, time and costs are not the only considerations in developing a symptom management intervention. If patients do not accept the intervention, then it is of little value. Further, certain subgroups of the patient population may benefit from a more extensive intervention, while other subgroups would do just as well with a simpler intervention. Answering the question about moderating effect is key to selecting the best interventions that tailor to patient characteristics, and ultimately to the development of more effective therapeutic approaches [1].

As Kraemer and colleagues have argued, moderating effects can be disguised [3]. A difficulty with moderating effects is that formal hypotheses are seldom presented and trials are rarely powered to test for moderating effects. As such, arguments to explain the moderating effects are largely post hoc and seldom flow from the conceptual framework upon which the trial is based. While no main effects were observed for the intervention arm, the difference existed in the patient's age in Trial II, and a similar pattern toward significance was observed in Trial I. Younger patients responded to educational approaches delivered by the AVR or a "coach" and older patients to nurse-delivered symptom management strategies. New strategies were presented in response to new symptoms that rose above threshold at successive contacts. Our evidence

reveals that younger patients appeared able to identify specific strategies from the SMT and to incorporate them into their daily lives resulting in improved symptom management. The oldest group of patients may, based on some evidence, possess less attention control and adaptability [44,45]. Therefore, they may value interactions with nurses who assist them to select and tailor interventions that address their symptoms in a manner that conforms to their daily schedules. The oldest patients in the "coach" or the AVR system, who were referred to the written guide, appeared less able to extract information and apply it to their personal situation to manage symptoms. In contrast, the youngest patients responded more favorably to classic written material that guided them to self-management approaches they could read and implement.

Further supporting the similarity of the effects of age in the two trials is the fact that the nurse, "coach," and AVR arms were tested on very similar samples of cancer patients undergoing chemotherapy. The significant age by trial arm interaction in Trial II and similar patterns in the adjusted means by trial arm and age in both trials strongly support the argument that older patients prefer the intervention utilizing interpersonal interactions with a nurse as compared to interactions with the AVR or a "coach" who refer them to a SMT. This difference may be based on the tailoring and support that nurses provide to older patients. In contrast, the younger patients may prefer approaches that allow them to read and act on information in their own styles. They may not want to invest the time or engage in extended conversations with nurses. They appear equally responsive to both the "coach" and the AVR because these arms drove the symptom severity lower than in the nurse arm. This suggests that their responsiveness is not due to a greater comfort with technology (there was no technology in the "coach" arm) but due to the relative simplicity of the intervention where symptoms were assessed, symptoms

above threshold were specified, and information was provided to the patients to draw upon as needed to manage symptoms.

We saw no differences in the numbers of symptoms reported by the oldest and youngest age groups, so it is unlikely that the educational approaches worked better for persons with fewer symptoms to manage. Further, even though Trial I required that patients report pain and/or fatigue at a specified severity and have a participating family caregiver in order to enroll, we found no differences in average number of symptoms between the two trials. Fatigue was the most prevalent symptom among all arms and pain while a bit higher in Trial I did not produce unique effects. Participation of a family caregiver with the patient in Trial I but not in Trial II may have impacted the outcomes. However, given the similar findings we believe such impacts are modest. The written strategies presented in the SMT were carefully measured so that reading and comprehension were at a 6^{th} grade level. We believe this may have helped reduce the effect of educational level on use of the SMT and allowed us to identify the moderating effects of age and not of education.

Finally, we found that higher levels of patients' depressive symptoms at intake resulted in poorer symptom management at week 10, regardless of the intervention arm. Thus, given a standard dose of the intervention in either arm, patients with CESD scores of 16 or higher responded less favorably than those with scores below 16. This appears consistent with reports by Given and colleagues [31], who indicated that patients with worse depressive symptoms required more contacts in order to respond to symptom management interventions.

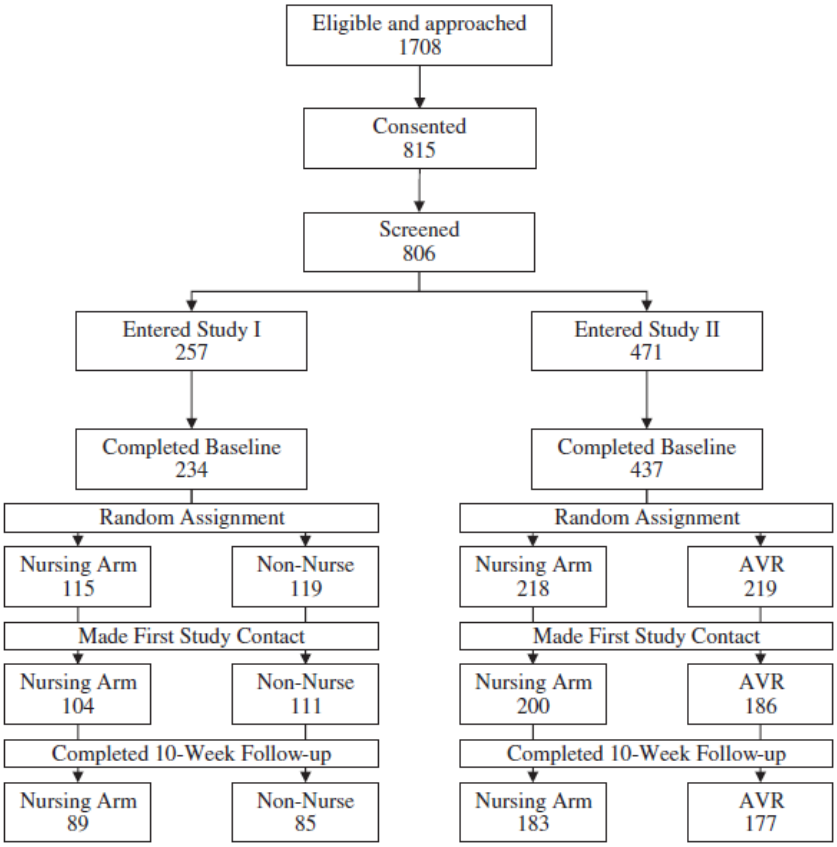

Figure 1. Flow chart showing progression of patients through the trials

Table Legends

1. Table 1: Baseline descriptive statistics by trial arm for the two trials
2. Table 2: Descriptive statistics for symptom severity and Center for Epidemiologic Studies – Depression (CESD) scores at intake and week 10 by trial arm for the two trials
3. Table 3: Summary of the model relating symptom severity at week 10 to severity at baseline, trial arm, and patient characteristics
4. Table 4: Least square means symptom severity at week 10, by age category and trial arm, adjusted for baseline severity and depressive affect

Table 1: Descriptive statistics by trial arm for the two trials

	Trial I		Trial II	
	Nurse N = 115 N (%)	"Coach" N = 119 N (%)	Nurse N = 218 N (%)	AVR N = 219 N (%)
Age				
≤ 45	12 (10)	16 (13)	40 (18)	33 (15)
46-55	32 (28)	30 (25)	56 (26)	68 (31)
56-65	38 (33)	41 (34)	72 (33)	69 (32)
66-75	27 (23)	20 (17)	36 (17)	27 (12)
> 75	6 (5)	12 (10)	14 (6)	21 (10)
Sex				
Male	47 (41)	47 (39)	57 (26)	53 (24)
Female	68 (59)	72 (61)	161 (74)	166 (76)
Race				
Caucasian	99 (88)	110 (92)	186 (86)	184 (86)
African American	10 (9)	7 (6)	27 (12)	22 (10)
Others	4 (3)	2 (2)	4 (2)	8 (4)
Education				
≤ High School	38 (33)	45 (38)	71 (33)	67 (31)
> High School - ≤ College	56 (49)	55 (46)	113 (52)	108 (49)
Graduate/ Professional	21 (18)	19 (16)	34 (16)	44 (20)
Marital Status				
Never Married	7 (6)	13 (11)	23 (11)	26 (12)
Married/Living Together	94 (82)	85 (72)	138 (63)	131 (59)
Divorced/ Separated/ Widowed	14 (12)	20 (17)	57 (26)	62 (29)
Employed				
Yes	31 (27)	30 (25)	67 (31)	74 (34)
No	84 (73)	89 (75)	151 (69)	145 (66)

Table 1 (Continued): Descriptive statistics by trial arm for the two trials

	Trial I		Trial II	
	Nurse N = 115 N (%)	"Coach" N = 119 N (%)	Nurse N = 218 N (%)	AVR N = 219 N (%)
Cancer Site				
Breast	27 (23)	30 (25)	90 (41)	87 (40)
Colon	10 (9)	8 (7)	30 (14)	32 (15)
Lung	34 (30)	35 (29)	37 (17)	34 (16)
Genitourinary	13 (11)	10 (8)	13 (6)	15 (7)
Gastrointestinal including pancreas	6 (6)	16 (13)	16 (7)	16 (7)
Other	25 (22)	20 (17)	32 (15)	35 (16)
Cancer Stage				
Early	8 (7)	13 (11)	31 (14)	44 (20)
Late	105 (93)	104 (89)	185 (86)	175 (80)
Metastasis				
Yes	75 (65)	69 (58)	128 (59)	112 (51)
No	40 (35)	50 (42)	90 (41)	107 (49)

Table 2: Descriptive statistics for symptom severity and Center for Epidemiologic Studies – Depression (CESD) scores at intake and week 10 by trial arm for the two trials

	Trial I				Trial II			
	Nurse		"Coach"		Nurse		AVR	
	Intake N = 115	Week 10 N = 89	Intake N = 119	Week 10 N = 85	Intake N = 218	Week 10 N = 183	Intake N = 219	Week 10 N = 177
Symptom Severity Mean (SD)	39.9 (21.0)	21.3 (17.9)	39.2 (22.9)	21.0 (16.6)	32.5 (20.9)	20.9 (19.1)	36.1 (22.8)	20.9 (17.9)
CESD Mean (SD)	12.9 (6.3)	9.7 (5.6)	14.1 (7.5)	10.4 (6.7)	12.3 (7.7)	10.0 (7.3)	12.9 (8.0)	9.5 (6.5)

Table 3: Summary of the model relating symptom severity at week 10 to severity at baseline, trial arm, and patient characteristics.

		Trial I				Trial II			
Source	DF	Type III SS	Mean Square	F Value	Pr > F	Type III SS	Mean Square	F Value	Pr > F
Symptom severity at baseline	1	5197	5197	20.62	<0.01	19451	19451	83.50	<0.01
Trial arm	1	35	35	0.14	0.71	26	26	0.11	0.74
CESD	1	1284	1284	5.09	0.03	1909	1909	8.19	<0.01
Age category	4	1089	272	1.08	0.37	521	130	0.56	0.69
Age category × Trial arm	4	1169	292	1.16	0.33	3658	914	3.93	<0.01
$F(11, 151) = 4.02$, $p < 0.0001$						$F(11,348) = 16.42$, $p < 0.0001$			

Table 4: Least square means symptom severity at week 10, by age category and trial arm, adjusted for baseline severity and depressive affect.

	Least Square Means from final model									
	Trial I					Trial II				
Age groups	Nurse		"Coach"		*p*-Value	Nurse		AVR		*p*-Value
	N	Mean	N	Mean		N	Mean	N	Mean	
≤ 45	12	29.28	16	19.16	0.15	32	30.39	27	15.63	<0.01
46-55	29	19.67	28	16.86	0.57	52	20.52	57	20.34	0.98
56-65	35	19.83	37	22.83	0.49	61	22.51	57	21.50	0.72
66-75	24	25.17	20	24.71	0.93	27	20.72	18	26.78	0.19
> 75	4	18.04	12	34.67	0.19	11	19.84	18	26.35	0.27

REFERENCES

1. Emsley R, Dunn G, White IR. Mediation and moderation of treatment effects in randomised controlled trials of complex interventions. *Stat Methods Med Res* 2010; **19** (3): 237-270.
2. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology* 1986; **51** (6): 1173-1182.
3. Kraemer HC, Frank E, Kupfer DJ. Moderators of treatment outcomes: clinical, research, and policy importance. *JAMA* 2006; **296** (10): 1286-1289.
4. Dale W, Mohile SG, Eldadah BA, et al. Biological, clinical, and psychosocial correlates at the interface of cancer and aging research. *J Natl Cancer Inst* 2012; **104** (8): 581-589.
5. Dillin A, Gottschling DE, Nystrom T. The good and the bad of being connected: the integrons of aging. *Curr Opin Cell Biol* 2014; **26C** 107-112.
6. Sorocco KH, Lauderdale S. *Cognitive Behavior Therapy with Older Adults: Innovations Across Care Settings.* Davis D (ed). Springer Publishing Company: New York, 2011.
7. Butler AC, Chapman JE, Forman EM, Beck AT. The empirical status of cognitive-behavioral therapy: a review of meta-analyses. *Clin Psychol Rev* 2006; **26** (1): 17-31.
8. Given CW, Sikorskii A, Tamkus D, et al. Managing Symptoms Among Patients With Breast Cancer During Chemotherapy: Results of a Two-Arm Behavioral Trial. *J Clin Oncol* 2008; **26** (36): 5855-5862.
9. Denis C, Lavie E, Fatseas M, Auriacombe M. Psychotherapeutic interventions for cannabis abuse and/or dependence in outpatient settings. *Cochrane Database Syst Rev* 2006; (3): CD005336.
10. Brown P, Clark MM, Atherton P, et al. Will improvement in quality of life (QOL) impact fatigue in patients receiving radiation therapy for advanced cancer? *Am J Clin Oncol* 2006; **29** (1): 52-58.
11. Gould RL, Coulson MC, Howard RJ. Cognitive behavioral therapy for depression in older people: a meta-analysis and meta-regression of randomized controlled trials. *J Am Geriatr Soc* 2012; **60** (10): 1817-1830.
12. Doorenbos A, Given B, Given C, Verbitsky N. Physical functioning: effect of behavioral intervention for symptoms among individuals with cancer. *Nursing Research* 2006; **55** (3): 161-171.
13. Arnedt JT, Cuddihy L, Swanson LM, et al. Randomized controlled trial of telephone-delivered cognitive behavioral therapy for chronic insomnia. *Sleep* 2013; **36** (3): 353-362.
14. Farronato NS, Dursteler-Macfarland KM, Wiesbeck GA, Petitjean SA. A systematic review comparing cognitive-behavioral therapy and contingency management for cocaine dependence. *J Addict Dis* 2013; **32** (3): 274-287.
15. Hamdan-Mansour AM, Constantino RE, Farrell M, et al. Evaluating the mental health of Jordanian women in relationships with intimate partner abuse. *Issues Ment Health Nurs* 2011; **32** (10): 614-623.
16. Knight SJ, Scheinberg A, Harvey AR. Interventions in pediatric chronic fatigue syndrome/myalgic encephalomyelitis: a systematic review. *J Adolesc Health* 2013; **53** (2): 154-165.
17. Sherwood P, Given BA, Given CW, et al. A cognitive behavioral intervention for symptom management in patients with advanced cancer. *Oncology Nursing Forum* 2005; **32** (6): 1190-1198.

18. Sikorskii A, Given CW, Given B, et al. Symptom management for cancer patients: A trial comparing two multimodal interventions. *Journal of Pain Symptom Management* 2007; **34** (3): 253-264.
19. Irwin MR, Cole JC, Nicassio PM. Comparative meta-analysis of behavioral interventions for insomnia and their efficacy in middle-aged adults and in older adults 55+ years of age. *Health Psychol* 2006; **25** (1): 3-14.
20. Rammstedt B, Rammsayer TH. Self-estimated intelligence: Gender differences, relationship to psychometric intelligence and moderating effects of level of education. *European Psychologist* 2002; **7** (4): 275-284.
21. Narayan S, Krosnick J. Education moderates some response effects in attitude measurement. *Public Opinion Quarterly* 1996; **60** (1): 58-88.
22. Joseph G, Beattie MS, Lee R, et al. Pre-counseling education for low literacy women at risk of Hereditary Breast and Ovarian Cancer (HBOC): patient experiences using the Cancer Risk Education Intervention Tool (CREdIT). *J Genet Couns* 2010; **19** (5): 447-462.
23. Addington-Hall J. The legacy of cancer on depression and anxiety. *Lancet Oncol* 2013; **14** (8): 675-676.
24. Krebber AM, Buffart LM, Kleijn G, et al. Prevalence of depression in cancer patients: a meta-analysis of diagnostic interviews and self-report instruments. *Psychooncology* 2014; **23** (2): 121-130.
25. Singer S, Szalai C, Briest S, et al. Co-morbid mental health conditions in cancer patients at working age - prevalence, risk profiles, and care uptake. *Psychooncology* 2013; **22** (10): 2291-2297.
26. Barsevick A, Beck SL, Dudley WN, et al. Efficacy of an intervention for fatigue and sleep disturbance during cancer chemotherapy. *J Pain Symptom Manage* 2010; **40** (2): 200-216.
27. Brothers BM, Yang HC, Strunk DR, Andersen BL. Cancer patients with major depressive disorder: testing a biobehavioral/cognitive behavior intervention. *J Consult Clin Psychol* 2011; **79** (2): 253-260.
28. Carpenter JS, Wu J, Burns DS, Yu M. Perceived control and hot flashes in treatment-seeking breast cancer survivors and menopausal women. *Cancer Nurs* 2012; **35** (3): 195-202.
29. Fors EA, Bertheussen GF, Thune I, et al. Psychosocial interventions as part of breast cancer rehabilitation programs? Results from a systematic review. *Psychooncology* 2011; **20** (9): 909-918.
30. Hart SL, Hoyt MA, Diefenbach M, et al. Meta-analysis of efficacy of interventions for elevated depressive symptoms in adults diagnosed with cancer. *J Natl Cancer Inst* 2012; **104** (13): 990-1004.
31. Given C, Given B, Rahbar M, et al. Does a symptom management intervention affect depression among cancer patients: results from a clinical trial. *Psychooncology* 2004; **13** (11): 818-830.
32. Edwards AG, Hulbert-Williams N, Neal RD. Psychological interventions for women with metastatic breast cancer. *Cochrane Database Syst Rev* 2008; (3): CD004253.
33. Akechi T, Okuyama T, Onishi J, Morita T, Furukawa TA. Psychotherapy for depression among incurable cancer patients. *Cochrane Database Syst Rev* 2008; (2): CD005537.
34. Jeon S, Given CW, Sikorskii A, Given B. The utility of screening in the design of trials for symptom management in cancer. *Journal of Pain & Symptom Management* 2009; **38** (4): 606-614.

35. Given B, Given C, Sikorskii A, et al. Establishing mild, moderate, and severe scores for cancer related symptoms: How consisten and clinically meaningful are interference based severity cut points? *Journal of Pain and Symptom Management* 2008; **35** (2): 126-135.
36. Sikorskii A, Given CW, You M, Jeon S, Given BA. Response analysis for multiple symptoms revealed differences between arms of a symptom management trial. *Journal of Clinical Epidemiology* 2009; **62** (7): 716-724.
37. Given C, Given B, Rahbar M, et al. Effect of a cognitive behavioral intervention on reducing symptom severity during chemotherapy. *Journal of Clinical Oncology* 2004; **22** (3): 507-516.
38. Radloff LS. The CES-D Scale: A self report depression scale for research in the general population. *Applied Psychological Measurement* 1977; **1** (3): 385-401.
39. Lewinsohn PM, Seeley JR, Roberts RE, Allen NB. Center for epidemiologic studies depression scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychology and Aging* 1997; **12** 277-287.
40. Decker V, Spoelstra S, Miezo E, et al. A pilot study of an automated voice response system and nursing intervention to monitor adherence to oral chemotherapy agents. *Cancer Nursing* 2009; **32** (6): E20-E29.
41. Spoelstra SL, Given BA, Given CW, et al. An intervention to improve adherence and management of symptoms for patients prescribed oral chemotherapy agents: an exploratory study. *Cancer Nursing* 2013; **36** (1): 18-28.
42. Given B, Given CW, Sikorskii A, et al. Analyzing symptom management trials: the value of both intention-to-treat and per-protocol approaches. *Oncology Nursing Forum* 2009; **36** (6): E293-302.
43. Given CW, Bradley C, You M, Sikorskii A, Given B. Costs of novel symptom management interventions and their impact on hospitalizations. *Journal of Pain & Symptom Management* 2010; **39** (4): 663-672.
44. Cashdollar N, Fukuda K, Bocklage A, et al. Prolonged disengagement from attentional capture in normal aging. *Psychol Aging* 2013; **28** (1): 77-86.
45. McVay JC, Meier ME, Touron DR, Kane MJ. Aging ebbs the flow of thought: adult age differences in mind wandering, executive control, and self-evaluation. *Acta Psychol (Amst)* 2013; **142** (1): 136-147.