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Fatigue During Breast Cancer Radiotherapy: An Initial Randomized Study of Cognitive–Behavioral Therapy Plus Hypnosis

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Objective: The study purpose was to test the effectiveness of a psychological intervention combining cognitive–behavioral therapy and hypnosis (CBTH) to treat radiotherapy-related fatigue. ***Design*:** Women ($n = 42$) scheduled for breast cancer radiotherapy were randomly assigned to receive standard medical care (SMC) ($n = 20$) or a CBTH intervention ($n = 22$) in addition to SMC. Participants assigned to receive CBTH met individually with a clinical psychologist. CBTH participants received training in hypnosis and CBT. Participants assigned to the SMC control condition did not meet with a study psychologist. ***Main Outcome Measures*:** Fatigue was measured on a weekly basis by using the fatigue subscale of the Functional Assessment of Chronic Illness Therapy (FACIT) and daily using visual analogue scales. ***Results*:** Multilevel modeling indicated that for weekly FACIT fatigue data, there was a significant effect of the CBTH intervention on the rate of change in fatigue ($p < .05$), such that on average, CBTH participants' fatigue did not increase over the course of treatment, whereas control group participants' fatigue increased linearly. Daily data corroborated the analyses of weekly data. ***Conclusion***: The results suggest that CBTH is an effective means for controlling and potentially preventing fatigue in breast cancer radiotherapy patients.

Keywords: radiotherapy, fatigue, breast cancer, hypnosis, cognitive-behavioral therapy

Over 182,000 American women will be diagnosed with breast cancer in 2008, and the vast majority of these women will undergo adjuvant radiotherapy. Although breast cancer radiotherapy increases disease-free survival and life expectancy, it is not without adverse consequences, chief among which is fatigue. Fatigue typically increases over the course of treatment (Irvine, Vincent, Graydon, & Bubela, 1998; Knobf & Sun, 2005), and has pervasive and detrimental effects on patients' physical, psychological, social, and occupational functioning (Curt, 2000; Jereczek-Fossa, Marsiglia, & Orecchia, 2002; Spelten et al., 2003). Fatigue is frequently rated as the most distressing symptom faced by breast cancer radiotherapy patients (Jereczek-Fossa, Marsiglia, & Orecchia, 2001), and is clearly an outcome worthy of clinical intervention.

There is mounting evidence that cognitive and emotional factors play pivotal roles in the experience of cancer-related fatigue. In terms of cognitive factors, both catastrophizing about fatigue (Jacobsen, Andrykowski, & Thors, 2004), and response expectancies for fatigue have been found to be positively related to level of experienced fatigue in breast cancer patients (Montgomery & Bovbjerg, 2001, 2004). In terms of emotional factors, there is a growing amount of research demonstrating a link between emotional distress and cancer-related fatigue (e.g., (Valentine & Meyers, 2001).

In combination, this literature suggests that a psychological treatment package designed to reduce catastrophizing, fatigue expectancies, and emotional distress in breast cancer radiation oncology patients would have the capacity to control the development of radiotherapy-related fatigue. More specifically, the literature suggests that a cognitive–behavioral therapy (CBT) intervention that includes a cognitive restructuring component (i.e., learning to reduce catastrophizing), and which is designed to

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reduce distress may prove to be beneficial for breast cancer radiotherapy patients. CBT has been found to be effective for managing fatigue symptoms in heterogeneous samples of patients undergoing medical treatments for cancer (Kangas, Bovbjerg, & Montgomery, 2008). Also, CBT approaches have been shown to effectively reduce levels of distress in cancer patients (Redd, Montgomery, & DuHamel, 2001). However, as noted earlier, CBT is not specifically designed to reduce response expectancies. Therefore, an additional treatment component that targets response expectancies might further control radiotherapy-related fatigue. Hypnosis is one such intervention.

During hypnosis, patients are given suggestions for relief from specific side effects, which change patients' expectations for those side effects, which in turn may directly lead to reductions in the experiences of those side effects (e.g., reduced fatigue) (Kirsch, 1990). The literature (Redd et al., 2001) has strongly supported the efficacy of hypnosis in controlling cancer treatment-related side effects, and more recent studies have documented the effects of hypnosis on fatigue in breast cancer surgery patients (Montgomery et al., 2007).

Meta-analytic results have demonstrated that CBT interventions that include a hypnosis component are significantly more effective than CBT interventions alone (Kirsch, Montgomery, & Sapirstein, 1995). Therefore, in order to maximize potential clinical benefit to patients, we chose to test an intervention that incorporated both these therapeutic treatment components.

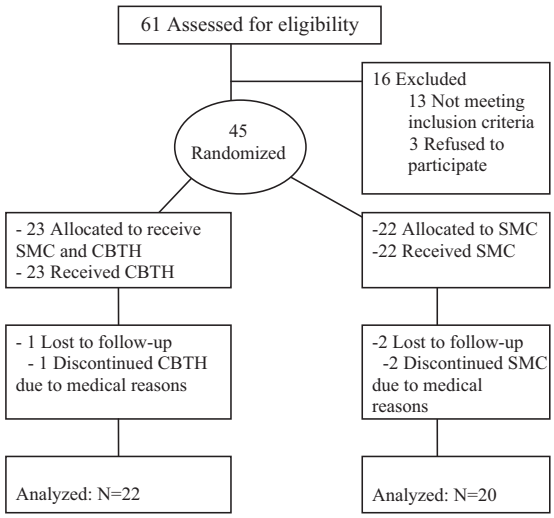
The objective of the present study was to test the effectiveness of an intervention combining cognitive–behavioral therapy and hypnosis (CBTH) to manage radiotherapy-related fatigue in a randomized clinical trial of breast cancer patients. As neuroticism (Michielsen, Van der Steeg, Roukema, & De Vries, 2007) and prior chemotherapy (Donovan et al., 2004) have been demonstrated to be related to fatigue in cancer patients, they were included as covariates. The hypothesis was that CBTH patients would have less fatigue relative to patients receiving standard medical care (SMC).

Method

Participants

Sample size for this preliminary study was based on published effect sizes for CBT plus hypnosis ($d = .66$) (Kirsch et al., 1995), as well as for hypnosis effects on fatigue in breast cancer patients specifically ($d = .84$) (Montgomery et al., 2007). With power set at .80, two-tailed alpha set at .05, using a repeated measures design, minimum total sample size was calculated at 42 participants (Faul, Erdfelder, Lang, & Buchner, 2007).

A total of 45 women were randomized, and 42 women completed this preliminary study: 22 in the CBTH group and 20 in the SMC control group (see Figure 1) for a retention rate of 93%. The institutional review board approved the project, and all participants completed written informed consent documents. Participants (see Table 1) were eligible for the present study if they were: scheduled for breast cancer radiotherapy; able to speak and read English (due to the fact that all the study measures and the study intervention were in English); over age 18; and willing to be randomized to study treatment group. Patients were excluded from the study if they had any uncontrolled comorbid psychiatric or medical illness (as determined by medical chart review) or if they had metastatic disease. Patients were recruited from an urban radiation oncology clinic from June 2006 to December 2007.



Note: CBTH = Cognitive behavior therapy plus hypnosis. SMC = standard medical care.

Figure 1. Study flowchart.

Measures

Weekly fatigue measure. The 13-item Functional Assessment of Chronic Illness Therapy–Fatigue Subscale (FS) was used to measure level of fatigue over the past week (Yellen, Cella, Webster, Blendowski, & Kaplan, 1997). The FS has demonstrated excellent internal consistency ($\alpha = .93$–$.95$), good test–retest reliability (.90), and validity has been repeatedly confirmed for this widely used scale in breast cancer patients (Yellen et al., 1997). Cronbach's alpha for the sample was .94.

Daily fatigue measure. Daily levels of fatigue were measured using a 100 mm visual analog scale (VAS). The item stated, "RIGHT NOW how fatigued do you feel? Please put a slash through this line to indicate how fatigued you feel." The line was anchored by "*Not at all fatigued*," and "*As fatigued as I could be*." The VAS format for the assessment of fatigue has received strong support in the literature on women undergoing procedures related to breast cancer (Geinitz et al., 2004; Montgomery et al., 2007) and is particularly useful in busy medical settings where patient burden and time constraints are common. VASs to assess "muscle weakness," another aspect of fatigue, were employed in an identical manner.

Possible covariates. Two variables were examined as possible covariates of fatigue. The first was neuroticism. Neuroticism has been demonstrated to be related to fatigue in cancer patients (Michielsen et al., 2007). The NEO-Five Factor Inventory Neuroticism Subscale (NEO-N) (Costa & McCrae, 1992) was used (short form, from the NEO-FFI) to assess neuroticism. The shortened form of the NEO-N (Costa & McCrae, 1992) is a widely used, well-validated, self-report questionnaire that contains 12 items and has good internal consistency ($\alpha = .86$). Cronbach's

Table 1
Medical and Demographic Background Characteristics of Participants by Group

	Group			
	CBTH (n = 22)		Control (n = 20)	
Variable	n (%)	M (SD)	n (%)	M (SD)
Education				
College degree or higher	15 (68)		8 (40)	
Less than college degree	7 (32)		12 (60)	
Marital status				
Currently married	14 (36)		9 (45)	
Not currently married	8 (64)		11 (55)	
Ethnicity				
Caucasian	16 (73)		10 (50)	
Not Caucasian	6 (27)		10 (50)	
Trait neuroticism		28.00 (8.31)		27.51 (6.81)
Chemotherapy prior to radiation				
Yes	12 (55)		11 (55)	
No	10 (45)		9 (45)	
Cancer stage				
Stage 2 or lower	15 (68)		11 (55)	
Stage 3	7 (32)		9 (45)	
Karnofsky performance status		98.75 (3.19)		96.57 (7.45)
age		53.45 (10.43)		52.78 (11.65)

Note. CTBH = cognitive–behavioral therapy and hypnosis. No factor was significantly different between the groups; all p's $> .05$.

alpha for the current sample was .83. The second covariate was history of chemotherapy, assessed via medical chart review. Prior chemotherapy was scored dichotomously (yes/no).

Self-reported demographic information was also collected from participants, and relevant medical history variables were abstracted from patients' medical charts, including their Karnofsky Performance Status (Karnofsky & Burchenal, 1949) upon beginning radiotherapy.

Procedure

Consecutive patients scheduled for breast cancer radiotherapy were referred by their radiation oncologist and completed informed consent documents. Data were collected prospectively. Participants completed the demographics questionnaire and the NEO-N prior to radiotherapy. Once treatment began, participants were asked to complete the FS on a weekly basis at home, and to turn in responses to a research assistant. VAS fatigue and muscle weakness measures were completed on a daily basis, at the same time each night (i.e., before going to bed). Participants turned in these forms on a daily basis (Monday through Friday) to a research assistant. Forms filled out over the weekend were returned on Monday mornings. Following informed consent, participants were randomly assigned to either the CBTH or to the SMC control group using computer-generated random positive integers. Randomization assignments were generated by the first author, who communicated with the interventionist on the morning of the intervention to assign the participant to a group. The sequence and assignments were unknown to the research assistants, who enrolled participants and collected all outcome data. As participants were active in the intervention, it was impossible to blind them to group assignment. Similarly, interventionists (n = 2) were not blind to group assignment, as they had to conduct the intervention. Interventionists were blind to all outcome data.

Intervention procedure. Patients in the CBTH group were told that the CBT component was based on the idea that how one thinks about an event can have emotional, behavioral, and physical consequences. The rationale provided for hypnosis was that hypnosis has been demonstrated to be effective for controlling symptoms associated with cancer and its treatment. On the day of their first preradiotherapy planning session, the interventionist met with each patient in a private room in the radiation oncology clinic to conduct a brief (15 minute) hypnosis session that consisted of (1) addressing common misconceptions about hypnosis; (2) a hypnotic induction including suggestions for mental and physical relaxation; (3) guided imagery of a peaceful and safe place; (4) suggestions for increased hypnotic depth; (5) and specific suggestions for reduced radiotherapy-related fatigue, reduced distress, increased sense of relaxation, increased well-being, and increased energy. Following these suggestions, patients were given a cue word for entering hypnosis on their own. The interventionist then ended the hypnosis session and gave participants a CD player and a prerecorded CD of the hypnosis intervention to listen to at home. Prior to patients' second pretreatment planning appointment, the therapist met with patients for 30 minutes and taught them CBT skills including how to recognize negative beliefs regarding radiotherapy and/or fatigue (e.g., catastrophizing); the emotional, behavioral, and physical consequences of those beliefs; how to debate such beliefs and change them to more helpful alternatives (Ellis, 1994); and how to practice behavioral strategies to manage treatment-related fatigue (including activity scheduling and exercise, as exercise has been demonstrated to be effective in reducing cancer-related fatigue (Kangas et al., 2008). Following this CBT session, participants were given a CBT workbook to review. They were also taught to complete a thought record worksheet (which typically takes less than five minutes to complete) and were asked to complete two of these worksheets per week (during the six-week course of their radiotherapy). The therapist then met with each patient twice per week (for a total of 12 sessions) in the radiation oncology clinic to go over these worksheets (5- to 15-minute sessions). Attendance was perfect, as participants were necessarily present in the radiation oncology clinic to receive their radiotherapy.

Participants randomly assigned to the SMC control group had no contact at all with the study interventionist. However, these participants completed daily and weekly fatigue measures. Participants assigned to the control group were offered the option of receiving a free intervention session at the conclusion of their study participation if they were interested. They were also given a CD player, so that provision of a CD player would be equivalent across groups. There were no adverse events in either study group.

Analytic procedure. The effect of the CBTH intervention on patients' radiotherapy-related fatigue (measured weekly and daily) was analyzed using multilevel modeling (MLM; Snijders & Bosker, 1999). For each covariate in the MLMs reported below, separate parameter estimates were generated for the impact of the covariate on initial status and linear rate of change. MLMs were

conducted using maximum likelihood estimation in the NLME package of R (version 2.5.1; R Development Core Team, 2007). The percent of variance explained by each MLM (i.e., R^2) was calculated (Roberts & Monaco, 2006). In addition, the proportion of variance accounted for by the CBTH intervention was calculated (Singer & Willett, 2003) and was then converted to Cohen's *d* using formulae described by Hunter and Schmidt (1990).

Trait neuroticism (NEO-FFI) and chemotherapy history were included as covariates in daily and weekly MLMs. In order to aid parameter interpretation, neuroticism and chemotherapy history scores were centered around their respective grand means (Kraemer & Blasey, 2004; Singer & Willett, 2003). Consequently, the intercept parameters for the initial status and rate of change model components represent the average initial symptom level and average rate of change, respectively, for control group participants, adjusting for neuroticism and chemotherapy history. Prior to analyzing the effect of the intervention on fatigue, race, marital status, level of education, cancer stage, interventionist, and KPS were compared across groups to ensure the adequacy of random assignment. Independent samples *t* tests (continuous variables) and Fisher's exact tests (categorical variables) indicated that no background variable differed across groups, *p*s>.05. In addition, no background variable had a significant effect on initial status or rate of change in any MLM reported below and were thus excluded from models.

Table 2
Effects of Neuroticism, Chemotherapy History, and the Intervention on Initial Fatigue Status and Rate of Change in Fatigue

	Effect on initial status (Week 1) of weekly FACIT fatigue	Effect on rate of change of weekly FACIT fatigue
Intercept	15.13***	1.57***
Intervention	.27	−1.51*
Predictor	.54*	.03
Chemotherapy history	6.03	−.33
	Effect on initial status (Day 1) of daily VAS fatigue	Effect on rate of change of daily VAS fatigue
Intercept	30.03***	.62***
Intervention	3.99	−.39*
Neuroticism	.97*	.00
Chemotherapy history	15.31*	.01
	Effect on initial status (Day 1) of daily VAS muscle weakness	Effect on rate of change of daily VAS muscle weakness
Intercept	16.90***	.49***
Intervention	−2.93	−.40*
Neuroticism	.92*	.01
Chemotherapy history	11.66†	−.20

Note. FACIT = Functional Assessment of Chronic Illness Therapy; VAS = visual analog scale. Intercept parameters represent the average initial status and rate of change for control participants, adjusting for neuroticism and chemotherapy history.
* $p < .05$. ** $p < .01$. *** $p < .001$. † $p < .10$.

Results

Weekly fatigue data

Individuals in the intervention group did not differ significantly from control participants in their level of fatigue at the first weekly assessment point, $p = .94$. Among control participants, weekly (FS) fatigue increased over time at the rate of 1.57 points per week, $t(146) = 3.58$, $p < .001$. However, over the course of radiation treatment, individuals in the intervention group had little increase in FS fatigue (only .06 points per week; see Figure 2), and the effect of the intervention on FS rate of change between the groups was significant, $t(146) = -2.49$, $p = .01$. Neuroticism had a significant effect on initial level of FS fatigue (Week 1), such that an increase of one point on the neuroticism scale was associated with a .54 point increase on the FS scale at Week 1, $t(38) = 2.10$, $p = .04$. Lastly, having chemotherapy prior to entering radiation was, on average, associated with a six-point higher score on the FS scale at Week 1, but this difference was not statistically significant, $p = .13$ (see Table 2). The weekly MLM model explained 51% of the variance in FS scores. The CBTH intervention accounted for 21% of the variance in weekly fatigue (Cohen's $d = .82$) (Hunter & Schmidt, 1990).

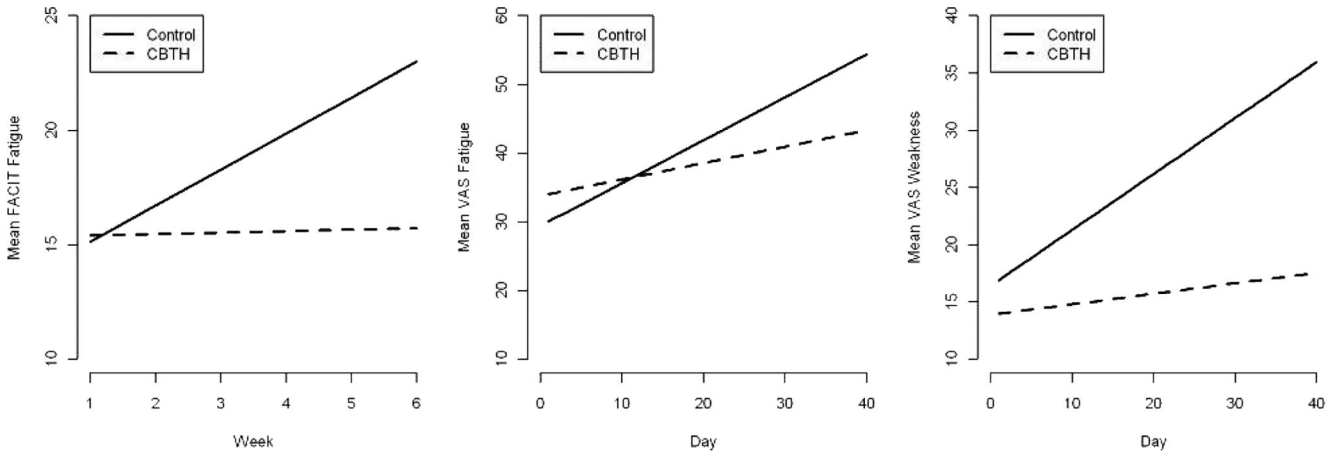


Figure 2. Effect of cognitive–behavioral therapy and hypnosis intervention on weekly and daily fatigue.

Daily fatigue and muscle weakness data

As with weekly data, chemotherapy history and trait neuroticism were included as covariates in the daily MLM. Fatigue increased over time among control participants, $t(1411) = 4.64$, $p < .001$, with their fatigue increasing an average of .62 points on the VAS scale each day (controlling for chemotherapy history and neuroticism). Although fatigue increased in the intervention group as well $t(1411) = -2.10$, $p = .04$, the rate of increase was significantly slower (see Table 2, Figure 2). Higher levels of trait neuroticism were associated with greater fatigue on Day 1 of radiotherapy, $t(38) = 2.33$, $p = .03$, such that each point increase on the neuroticism measure was associated with a one-point increase in initial VAS fatigue (see Table 2). Individuals who entered the study following chemotherapy had significantly higher fatigue at Day 1 (approximately 15 VAS points, on average), $t(38) = 2.44$, $p = .02$, but did not vary in their rate of change in fatigue scores over time, $p = .97$. The multilevel model for daily fatigue explained 21% of the variance in VAS fatigue scores. The CBTH intervention accounted for 13% of the variance in VAS fatigue ($d = .65$).

A similar pattern of effects was observed for daily muscle weakness. Muscle weakness increased significantly for both control participants, $t(1379) = 3.61$, $p < .001$, and CBTH participants, $t(1379) = -2.13$, $p = .03$, over time. However, the rate of increase in the CBTH group was significantly lower (see Table 2, Figure 2). Also, trait neuroticism predicted initial muscle weakness, $t(38) = 2.13$, $p = .04$, such that each point increase on the neuroticism measure was associated with a .92-point increase in Day 1 VAS muscle weakness (see Table 2). Individuals who entered the study following chemotherapy reported muscle weakness approximately 12 VAS points higher (see Table 2), on average, than patients who had not previously had chemotherapy, though this difference was not significant, $t(38) = 1.80$, $p = .08$. The MLM for daily muscle weakness ratings explained 30% of the variance in muscle weakness scores. The CBTH intervention accounted for 9% of the variance in muscle weakness ($d = .59$).

Analyses were repeated according to intent-to-treat guidelines (DeMets, 2004), and no differences in the pattern of results were found in contrast to the results presented earlier.

Discussion

The present randomized clinical trial demonstrated that an intervention combining cognitive–behavioral therapy and hypnosis (CBTH) was effective for controlling fatigue in breast cancer radiotherapy patients. Both weekly data and daily data supported this conclusion. It appears that the intervention prevented increases in fatigue during radiotherapy. The results also indicated that the beneficial effects of the intervention were independent neuroticism or prior chemotherapy effects, suggesting the potential generalizability of the effects of CBTH. The results are consistent with the clinical benefits of combining CBT with hypnosis (Kirsch et al., 1995), and CBTH effect sizes reported here (d ranged from .59 to .82) compare favorably with those reported in the broader cancer-related fatigue literature ($d = .31$) (Kangas et al., 2008). The results support further study of the broader clinical effectiveness, as well as underlying mechanisms, of the present CBTH intervention.

The present study has at least three limitations. First, our treatment was compared with an SMC control condition. Therefore, beneficial intervention effects could potentially be due to nonspecific factors (e.g., professional attention). However, one should note that the purpose of the present study was to investigate preliminary clinical benefit (which was demonstrated), not to examine underlying psychological mechanisms. Similarly, based on the design of the intervention, and the literature (Kirsch et al., 1995), one can speculate that both of the components of the present CBTH intervention contributed to clinical effects (Kirsch et al., 1995). However, confirming this hypothesis and determining the "active ingredients" of this intervention is an important area for future research. Second, the present study is limited by sample size. Although the effect sizes were consistently in the large range, the intervention effects should be replicated in a larger sample. Sample size also limited our ability to pursue mediational analyses with sufficient statistical power. Third, patients were not blind to treatment condition. As we were testing a psychological intervention, it was not possible to blind patients as they were required to be active participants in the intervention.

In conclusion, this initial test of CBTH to control fatigue during radiotherapy for breast cancer suggests that this intervention is effective for controlling, and perhaps even preventing, the development of fatigue in patients undergoing radiation treatment for breast cancer. To our knowledge, this is the first study to demonstrate prevention of increases in fatigue over the course of breast cancer radiotherapy, as well as the first study to demonstrate the effectiveness of a CBT plus hypnosis intervention for radiotherapy-related fatigue. Therefore, beneficial effects seen here merit further study to improve the quality of life of breast cancer radiotherapy patients.

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