Cancer-related Fatigue, Depressive Symptoms, and Functional Status: A Mediation Model

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Barsevick AM, Dudley WN, Beck SL. (2006). Cancer-related fatigue, depressive symptoms, and functional status: a mediation model. *Nurs Res*, *55*(5), 366-72.

Abstract:

Background: Patients with cancer grapple with a confusing array of disease- and treatment-related symptoms while trying to maintain functioning in usual roles and daily activities. Research is needed to sort out and identify symptom clusters as a basis for a rational approach to symptom management.

Objective: The aim of this study was to test, through secondary analysis, a mediation hypothesis about the direct and indirect relationships between fatigue and depressive symptoms through a pathway involving functional status.

Methods: Data from the experimental and control groups of a randomized clinical intervention trial for fatigue management, collected after the second chemotherapy treatment or during the last week of radiotherapy, were analyzed. The mediation pathway from fatigue to depressive symptoms through functional status was tested separately for groups receiving either an energy conservation intervention or a control intervention, equating for time and attention.

Results: For the control group, the results indicate support for partial mediation. The previously significant relationship between fatigue and depressive symptoms was reduced after functional status was controlled, accounting for 43% of the total mediated effect. The mediation hypothesis was not supported in the energy conservation group, indicating that the intervention may have changed the role of functional status in mediating the effect of fatigue on depressive symptoms.

Discussion: In the control group, when routine activities became more difficult because of fatigue, individuals had more depressive symptoms. The results suggest that functional status is an important factor to consider in symptom management for fatigue. An appropriate intervention for fatigue would have two targets: the fatigue and strategies to reduce the likelihood of impaired functioning that could result in elevated depressive symptoms.

Keywords: depressive symptoms, fatigue, functional status, symptom clusters

Article:

Individuals undergoing cancer treatment grapple with a confusing array of disease- and treatment-related symptoms while trying to maintain functioning in usual roles and daily activities. However, most research has been used to evaluate strategies for the management of individual symptoms such as pain (Miaskowski, Dodd, West, et al., 2004), fatigue (Yates et al., 2005), or depression (Barsevick, Sweeney, Haney, & Chung, 2002). Given the complexity of the

symptom experience for individuals undergoing cancer treatment, research is needed to begin to sort out and identify symptom clusters as a basis for a rational approach to the management of multiple symptoms (Barsevick, Whitmer, Nail, Beck, & Dudley, 2006).

Presented here is a secondary analysis of data from a randomized clinical trial (RCT) of a fatigue management intervention during cancer therapy (Barsevick et al., 2004). Two cancer symptoms (fatigue and depression) were examined as a symptom cluster to identify the mechanism by which these two symptoms could be related. Both a direct association between the symptoms and an indirect relationship through a mediation pathway involving functional status, an important outcome in symptom management, were proposed. It was also proposed that there would be differences in the mediation results for the experimental and control groups.

Symptom Clusters

The identification of symptom clusters in medicine is not new. Before the 20th century, the diagnosis of illness was based largely on the systematic observation of clusters of signs and symptoms. More recently, in oncology, there has been a call to examine symptom clusters as a way of making sense of the complex cancer symptom experience (Dodd, Janson, et al., 2001; Dodd, Miaskowski, & Paul, 2001). Although there is no accepted definition of symptom cluster, Dodd defined it as concurrent and related symptoms (Dodd, Miaskowski, & Paul, 2001). Miaskowski (2004) has suggested that relationships among symptoms within a cluster could include a common mechanism or etiology, shared variance, or the production of outcomes that differ from individual symptoms. In this presentation, the focus is on the mechanism by which two symptoms could have an influence on one another.

Research examining symptom clusters reflects an empirical search for common elements among individual symptoms that can link them as members of a cluster. Numerous studies have been used to demonstrate shared variance between symptom pairs, which has been described as an indicator of symptom clustering (Miaskowski, Dodd, & Lee, 2004). Correlation studies have included fatigue-insomnia (Beck & Schwartz, 2000; Miaskowski & Lee, 1999), fatigue-depression (Dodd, Miaskowski, et al., 2001; Loge, Abrahamsen, Ekeberg, & Kaasa, 2000; Miaskowski & Lee, 1999; Redeker, Lev, & Ruggiero, 2000), fatigue-pain (Beck & Schwartz; Dodd, Miaskowski, et al., 2001; Gaston-Johansson, Fall-Dickson, Bakos, & Kennedy, 1999), and pain-depression (Gaston-Johansson et al., 1999).

More recently, investigations have explored the mechanisms by which symptoms could influence one another. The direct and indirect relationships among symptoms and other variables have been explored through the use of mediation analysis. As defined by Baron and Kenny (1986), a mediator is a variable that accounts for the relationship between two other variables. Beck, Dudley, and Barsevick (2005) showed that one symptom could influence another symptom through its effect on a third symptom. A partial mediation model demonstrated that pain influenced fatigue directly and indirectly through an effect on sleep. That is, people who were in pain had poorer sleep quality, resulting in higher levels of fatigue. This model suggested that interventions for managing pain and reducing fatigue must also consider the individual's sleep quality.

Although symptom clusters have been described without a specific theoretical basis, the concept easily fits into a number of theories, including the Theory of Unpleasant Symptoms (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). This theory is used to address potential associations between and among multiple symptoms by asserting that symptoms can be related in complex ways, including mediated pathways. Also asserted is that symptoms can influence and be influenced by outcomes such as functional status.

Functional Status Outcomes Associated With Symptoms

From the standpoint of oncology nursing, functional status is an important outcome that is influenced by symptoms and symptom management. Functional status refers to one's ability to engage in usual activities and perform usual roles (Leidy, 1994). The variance in functional status has been accounted for by a set of symptoms (Dodd, Miaskowski, et al., 2001; Gaston-Johansson et al., 1999; Gift, Jablonski, Stommel, & Given, 2004). Given, Given, Azzouz, and Stommel (2001) demonstrated that the presence of specific symptoms had differential effects on functional status. Compared with individuals who had no pain, fatigue, or insomnia, those with one, two, or all three symptoms were incrementally less likely to be functioning well 6-8 weeks after the diagnosis of cancer. In an RCT of a nursing intervention for pain and fatigue management, the group who received the symptom intervention had lower symptom severity and improved physical and social functioning (Given et al., 2004; Given, Given, Azzouz, Kozachik, & Stommel, 2001).

Functional status has been linked to the symptom cluster of pain and depression through a mediation pathway (Williamson & Schulz, 1995). In a sample of outpatients with cancer, using a longitudinal analysis, it was shown that increased pain over time resulted in restriction of activities (an indicator of functional status), which predicted increased depressive symptoms. The findings demonstrated that pain and depressive symptoms were related directly and indirectly through their association with functional status. The results suggested that it was not the degree of pain that affected emotional well-being but the degree of disability that accompanied it. Other symptoms, such as fatigue and depression, could be related indirectly through a similar pathway involving functional status.

Fatigue and Depressive Symptoms as a Symptom Cluster

Fatigue and depression have been documented often as concurrent, related symptoms in patients with cancer. Of a sample of 987 patients with lung cancer enrolled in three chemotherapy clinical trials, 33% had sufficient depressive symptoms for them to be classified as depressed (Hopwood & Stephens, 2000). Fatigue was documented as an independent predictor of depression and functional impairment. Newell, Sanson-Fisher, Girgis, and Ackland (1999) documented that depressive symptoms were a significant problem for 23% of the participants in a sample of 201 oncology patients undergoing chemotherapy. Physical symptoms were associated with depressive symptoms in this sample, and fatigue was one of the most common symptoms reported. In 457 persons with Hodgkin's disease, 26% had fatigue for 6 months or longer; these were defined as fatigue cases (Loge et al., 2000). Fatigue correlated moderately with depressive symptoms ($r = .41$). Fatigue cases had higher levels of depressive symptoms than those not defined as cases.

Fatigue, depressive symptoms, and functional status were chosen for this analysis for several reasons. First, fatigue was a primary outcome in the parent study, which was reported by 97% of the study participants during cancer treatment. Depression was also a highly prevalent symptom, which was reported by 65% of the participants. Functional status was a primary outcome in the parent study. Although the experimental intervention reduced fatigue, it did not have a direct effect on functional status. However, it is possible that fatigue and functional status were part of a more complex mediation pathway involving depressive symptoms, as suggested by Williamson and Schulz (1995) in their analysis of pain and functional status. Using data from an RCT, it is possible to examine the differences in the proposed pathway for the experimental and control groups. Therefore, it was proposed that functional status was a mediator between fatigue and depressive symptoms in the control group but not in the group who received the intervention.

METHODS

Design and Sample

This study was a secondary analysis of data from an RCT of an energy conservation intervention for managing fatigue during cancer therapy (Barsevick et al., 2004). Individuals were included in the clinical trial if they were initiating at least three cycles of chemotherapy (CTX), 6 weeks of radiation therapy (RT), or concurrent treatment (CTX/RT) and any previous treatment was at least 1 month before current treatment. The sample of the RCT consisted of 396 individuals treated for breast, lung, colorectal, advanced prostate, gynecologic, or testicular cancer or lymphoma. Criteria for exclusion were the following: treatment with stem cell transplantation or biotherapy, overt evidence of a psychiatric disorder, or initiation of treatment of anemia or depression during the past 3 weeks.

Data on all participants in the RCT were collected before treatment. For the CTX or CTX/RT groups, follow-up data were collected 48 hr after the second and third cycles of chemotherapy. For the RT group, follow-ups occurred during the last week of radiation and 4 weeks after the completion of radiation. These time points have been documented as times of high fatigue during cancer treatment (Berger, 1998; Schwartz et al., 2000). Study participants received either a semistructured intervention focused on energy conservation and activity management (ECAM; n = 200) or a control intervention consisting of information on a healthy diet (n = 196).

The primary aim of the RCT was to test the effect of the energy conservation intervention on fatigue and functional status. In the clinical trial, it was demonstrated that the ECAM (experimental) group had significantly lower fatigue, but there was no difference between the ECAM group and the control group with regard to functional status. A secondary aim of the RCT was to examine the interrelationships among fatigue, other symptoms, and functional status. The study protocol of the parent study was approved by the institutional review board in accordance with federal regulations, and informed consent was obtained from all study participants. No additional approval or consent was required for the secondary analysis because the original consent form covered this aim of the RCT.

In keeping with the secondary aim of the RCT, this secondary analysis was undertaken to examine the direct and indirect relationships between fatigue and depressive symptoms, including a mediation pathway involving functional status. Data from the first follow-up point (48 hr after the second round of chemotherapy or the last week of radiation) were used. Separate

hypotheses were proposed for the experimental and control groups. The control group intervention was intended to equate for time and attention but was not expected to influence the relationships among fatigue intensity, functional status, and depressive symptoms. In the secondary analysis for the control group, it was proposed that fatigue would influence depressive symptoms through a relationship with functional status as described by Williamson and Schulz (1995). That is, as fatigue increased, functional status was expected to worsen, resulting in more depressive symptoms. Because the ECAM group learned skills designed to lessen the impact of fatigue on functioning, it was proposed that functional status in the context of higher fatigue would not be associated with depressive symptoms.

Independent Variables

Fatigue Intensity

The General Fatigue Scale, a seven-item scale, was designed for the RCT to capture fatigue impact at specific times, including fatigue today, most days, the past 48 hr, and in general (Meek, Nail, & Jones, 1997). Two additional items were used to address distress due to fatigue and its impact on daily activities. For the secondary analysis, a mean was computed for the five fatigue intensity items (Table 1). The distress and impact items were excluded from the analysis to avoid confounding with the mediator and outcome variables. Cronbach's [alpha] reliability for this sample was .95. Evidence of validity of this scale included sensitivity to change in activity levels ($p < .001$) and a factor analysis demonstrating a single factor (Meek et al., 1997).

Variable	Measure	RCT	Secondary Analysis
Fatigue	General Fatigue Scale	Dependent variable Seven items Five intensity items Two distress, impact items	Independent variable Five intensity items
Functional status	Functional Performance Inventory	Dependent variable 65 items, six subscales Body care Household activities Physical exercise Recreation Spiritual activities Social activities	Independent variable 18-Item household activities subscale
Depressive symptoms	Profile of Mood States Depressive Symptoms Scale	Covariate Five-item Depressive Symptoms Scale	Dependent variable Five-item Depressive Symptoms Scale

Note. RCT = randomized clinical trial of energy conservation.

TABLE 1. Variables Selected for the RCT and Secondary Analysis

Functional Status

In the RCT, the Functional Performance Inventory (FPI; Leidy, 1994), a 65-item scale with six subscales, was used to measure impairment of functional status due to treatment. Many items on the subscales had responses of "not applicable" because they were not relevant to the participant's usual activities. The 21-item household activities subscale had the fewest items

rated as not applicable; thus, it was chosen for the secondary analysis (Table 1). Ratings for items such as "grocery shopping" included "doing with no, some, or much difficulty" (scored as 3, 2, and 1, respectively) and "don't do for health reasons" (scored as 0). An item analysis of the 21 items revealed 3 items rated by most respondents as not applicable. These 3 items were eliminated from the analysis. The score for household activities was computed by averaging the values across the 18 remaining items. Higher scores reflected less impaired functioning. The reliability and validity of the FPI have been demonstrated (Larson, Kapella, Wirtz, Covey, & Berry, 1998; Leidy, 1999). The internal consistency reliability computed for this sample was high; Cronbach's [alpha] = .95.

Dependent Variable

Depressive Symptoms

The Short Form of the Profile of Mood States (POMS-SF; McNair, Lorr, & Droppleman, 1992) is a 30-item adjective checklist measuring the intensity of symptoms during the past week; there are six subscales. For this analysis, the five-item depressive symptom subscale was used (Table 1). Numerous studies have established the validity and reliability of POMS-SF and the subscales in patients with cancer (Barsevick et al., 2002). Responses to the adjective checklist ranged from 1, not at all, to 5, extremely. The internal consistency of the POMS depression subscale was high; Cronbach's [alpha] = .86.

Data Analysis

Hierarchical multiple regression analyses were conducted to test the mediating effect of functional status on the relationship between fatigue and depression. Functional status would serve as a mediator if it accounted for all or some of the relationship between fatigue and depressive symptoms. In testing for mediation, the procedure set forth by Baron and Kenny (1986) was followed. Mediation was inferred when the following criteria were met: (a) the direct relationship between the predictor (fatigue) and outcome variable (depressive symptoms) was significant; (b) the predictor was significantly related to the mediator (functional status); (c) the mediator was significantly related to the outcome variable; and (d) a previously significant direct relationship between the predictor and outcome variable was reduced in magnitude after the mediator was controlled. If the relationship between the predictor and outcome variable was no longer significant after controlling the mediator, the mediation effect would be considered complete; if the relationship remained but its significance was reduced, the mediation effect would be considered partial. The mediation pathway was evaluated using the Sobel (1982) test, used to test the hypothesis that the indirect pathway from fatigue to depressive symptoms through functional status is different from 0 (Dudley, Benuzillo, & Carrico, 2004). Separate regression analyses were conducted for each intervention condition (ECAM vs. control group; MacKinnon, 1994). For each group, fatigue scores were entered as predictors, depressive symptom scores were entered as outcome variables, and functional status scores were entered as mediators.

RESULTS

The experimental and control groups did not differ at baseline with regard to demographic (Table 2) or clinical (Table 3) factors. The results of the mediation analysis for the control and experimental groups are provided in Table 4. For the control group, the results indicated that functional status after cancer therapy mediated the relationship between fatigue and depressive

symptoms. A significant path from fatigue to depressive symptoms ([beta] = .34, $p < .001$), from fatigue to functional status ([beta] = -.45, $p < .001$), and from functional status to depressive symptoms ([beta] = -.41, $p < .001$) was demonstrated. Furthermore, the previously significant relationship between fatigue and depressive symptoms was reduced after functional status was controlled ([beta] = .19, $p = .02$), and results of the Sobel test indicated that this indirect effect was significant ($t = 3.34$, $p < .001$). The results support a partial mediation model in the control group, accounting for 43% of the total mediated effect.

Variable	ECAM Group (n = 144) n (%)	Control Group (n = 151) n (%)
Age (years)	M = 55.8 (SD = 13.10)	M = 56.9 (SD = 11.80)
Gender		
Females	125 (87)	133 (88)
Males	19 (13)	18 (12)
Ethnicity		
White	132 (92)	138 (91)
Non-White	12 (8)	13 (9)
Education		
No College	91 (63)	98 (65)
College	50 (35)	53 (35)
Unknown	3 (2)	
Marital Status		
Married	94 (65)	114 (76)
Unmarried	47 (33)	37 (24)
Unknown	3 (2)	
Work Status		
Working	69 (48)	69 (45)
Not working	75 (52)	82 (54)
Study Site		
FCCC	96 (67)	93 (62)
UU	48 (33)	58 (38)

TABLE 2. Demographic Characteristics of the Sample (N = 295)

Variable	ECAM Group (n = 144) n (%)	Control Group (n = 151) n (%)
Diagnosis		
Breast	109 (76)	114 (76)
Lung	17 (12)	23 (15)
Lymphoma	10 (7)	6 (4)
Colorectal	4 (3)	4 (3)
GU or GI	4 (3)	4 (3)
Stage (AJCC)		
0	9 (6)	14 (9)
1	51 (36)	45 (30)
2	46 (33)	52 (35)
3	23 (16)	24 (16)
4	10 (7)	14 (9)
Unavailable	5 (4)	2 (1)
Treatment		
Chemotherapy only	65 (45)	71 (47)
Radiation therapy only	70 (49)	65 (43)
Concurrent therapy	9 (6.3)	15 (10)

Notes. ECAM = energy conservation and activity management; GU = genitourinary; GI = gastrointestinal; AJCC = American Joint Committee on Cancer.

TABLE 3. Clinical Characteristics of the Sample

TABLE 4. Regression Coefficients for Mediation Analysis

	Fatigue to Depressive Symptoms				Fatigue to Functional Status				Functional Status to Depressive Symptoms				Fatigue to Depressive Symptoms Controlling for Functional Status			
Group	*B*	*SE*	β	*p*	*B*	*SE*	β	*p*	*B*	*SE*	β	*p*	*B*	*SE*	β	*p*
Control[a] (*n* = 151)	.11	0.03	.34	<.001	−.10	0.02	−.45	<.001	−.62	0.11	−.41	<.001	.06	0.03	.19	.02
ECAM[b] (*n* = 144)	.13	0.03	.39	<.001	−.11	0.02	−.50	<.001	−.47	0.12	−.30	<.001	.11	0.03	.31	.001

Notes. ECAM = energy conservation and activity management.
[a]Control group: Sobel value = 3.34, $p < .001$, percentage of total effect mediated = 43%.
[b]ECAM group: Sobel value = 1.56, $p = .12$.

For the ECAM group, fatigue was associated with depressive symptoms ([beta] = .39, p < .001); fatigue was also related to functional status ([beta] = -.50, p < .001), and functional status was associated with depressive symptoms ([beta] = -.30, p < .001). However, controlling functional status did not significantly reduce the relationship between fatigue and depressive symptoms ([beta] = .31, p = .001), and the Sobel test was not significant. Thus, the mediation model failed in the ECAM group because the condition of a change in the relationship between the mediator and the outcome was not met.

Discussion

In the control group, as predicted, the mediation hypothesis was supported. Higher fatigue in the context of poorer functioning was related to a higher level of depressive symptoms. When increased fatigue made routine household activities more difficult, depressive symptoms increased. This finding is in agreement with the results for the mediating role of functional status with regard to symptoms in another cancer sample (Williamson & Schulz, 1995). This result suggests that depressive symptoms were more likely to be elevated in individuals whose functional status was impaired by fatigue and who did not have the skills needed to minimize fatigue impact.

The same associations were tested for the ECAM group, who had been taught a common-sense coping skill to conserve energy. In this group, the mediation hypothesis was not supported. Although the direct associations between fatigue and functional status, between fatigue and depressive symptoms, and between functional status and depressive symptoms were significant, controlling for functional status did not add to the explanation of the relationship between fatigue and depressive symptoms. Compared with the finding for the control group, this result suggests that the pathway from fatigue to depressive symptoms through functional status had been disrupted by the ECAM intervention.

This mediation analysis allowed consideration not only of changes in individual outcomes due to an intervention but also of changes in the relationships between variables. The results of the secondary analysis suggest that functional status is an important factor to consider in symptom

management for fatigue because of its relationship with depressive symptoms. Based on these findings, an appropriate intervention for fatigue would have two targets: the fatigue and functional status. Teaching energy conservation strategies to patients with cancer undergoing treatment seems to have provided the skills needed to reduce fatigue and changed the relationship between functional status and depressive symptoms. The intervention could have served to reinforce the normalcy of fatigue as an expected, temporary symptom caused by treatment such that individuals undergoing cancer treatment did not become discouraged or depressed when they were less able to function in their usual activities. It is also possible that it enabled individuals with fatigue to set priorities to ensure that valued or important activities were continued and less important activities were let go.

Although these results are promising, it is important to note that this was a secondary analysis of cross-sectional data from one time point after the ECAM or control intervention (Clarke & Cossette, 2000). As in the parent study, there was sampling bias due to missing data in both the experimental and control groups, with individuals in poorer health less likely to provide complete data (Barsevick et al., 2004). Also, the results only demonstrate associations among the variables of interest; causal relationships cannot be assumed because the secondary analysis focused on only one time point. Research is needed to examine the mediation hypothesis prospectively in other samples receiving interventions for symptom management.

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