Nutritional, Functional, and Emotional Characteristics Related to Fatigue in Patients During and After Biochemotherapy

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Purpose/Objectives: To test Winningham's psychobiologic entropy hypothesis in patients receiving biochemotherapy for melanoma.

Design: Descriptive, correlational, cross-sectional study.

Setting: Midwest cancer center.

Sample: 25 male and female patients who were receiving biochemotherapy or who had completed treatment 6–12 months prior.

Methods: Data were collected using a series of questionnaires and diet recall.

Main Research Variables: Fatigue, anxiety, depression, distressing symptoms, nutritional intake, and weight.

Findings: Moderate fatigue was significantly related to physiologic and psychological symptoms but not to nutrient intake. The sample was overweight, and a significant number of participants were obese. High caloric intakes were evident. Depression was a significant problem.

Conclusions: Fatigue was not as severe as expected, but problems with responses to the fatigue scale may explain this. Nutritional status and nutrient intake were not correlated to fatigue in this sample. Activity levels were related to fatigue, and treatment reduced activity. On average, activity returned to pretreatment levels 6–12 months after treatment. Winningham's hypothesis held and will be useful for understanding fatigue in this population.

Implications for Nursing: Depression needs to be assessed and treated as a side effect of biotherapy. Assessing the impact of nutrition when patients are overweight or obese is difficult. A scale specifically designed to test Winningham's hypothesis is needed.

Key Points . . .

- ➤ Fatigue diminished and activity levels resumed 6–12 months after biochemotherapy for a variety of cancers.
- ➤ Depression is a known side effect of biotherapy, and patients need comprehensive assessment and treatment to manage this distressing symptom.
- ➤ The relationship between nutrient intake and fatigue in overweight or obese patients is difficult to establish.

Fatigue is one of the most frequently reported symptoms of cancer and cancer treatment (Balducci & Extermann, 2000; Beach, Siebeneck, Buderer, & Ferner, 2001; Fleming et al., 2003; Stasi, Abriani, Beccaglia, Terzoli, & Amadori, 2003). It can be the first sign of an underlying disease process, and subsequent treatment with surgery, radiotherapy, or chemotherapy can induce or exacerbate feelings of fatigue (Piper, Lindsey, & Dodd, 1987; Smets, Garssen, Schuster-Uitterhoeve, & de Haes, 1993; Wheeler, 1997).

Biotherapy is defined as "treatment with agents derived from biologic sources and/or affecting biologic responses" (Reiger, 1997, p. 574). Specifically, these biologic response modifiers are defined as "agents or approaches that modify the relationship between tumor and host by modifying the host's biologic response to tumor cells with a resultant therapeutic effect" (Mahich & Fefer, 1983, p. 63). Interferon alpha, a prototypical biotherapy agent, causes fatigue in 70% of patients (Stasi et al., 2003). When combined treatment with interleukin and interferon is given, an additive effect of perception of fatigue occurs with almost 100% of patients reporting the symptom (Figlin, Belldegrun, Moldawer, Zeffren, & deKernion, 1992; Hirsh et al., 1990). The fatigue resulting from biotherapy has been described, similarly to other cancer-related fatigue, as chronic, characterized by generalized weariness, weakness, exhaustion, and feelings of tiredness (Skalla & Reiger, 1995; Wheeler, 1997).

Biotherapy in combination with chemotherapy has demonstrated significant improvement in the median and long-term survival of patients with melanoma. The toxicities associated with treatment from the initial human trials of recombinant interferon alpha have been described as dose limiting, with fatigue being cited as the most important symptom (Cuaron & Thompson, 1995; Parkinson, 1989; Quesada, Talpaz, Rios, Kuzrock, & Gutterman, 1986). A greater understanding of fatigue in patients with melanoma receiving biotherapeutic agents is imperative because of the improvements in survival.

Donnelly's (1998) study of patients with melanoma receiving high-dose interferon alpha-2b used data from the Eastern Cooperative Oncology Group trial E1684. Patients first received the interferon via IV for four weeks, followed by 48 weeks of subcutaneous injections. A total of 280 patients participated, and fatigue was found to affect 96% of the population; 33% of

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those affected experienced grade 3 (moderate) fatigue, and 6% suffered grade 4 (severe) symptoms. Also, fatigue was cited as the reason that 12 patients discontinued treatment.

Dean et al. (1995) used a qualitative approach to describe the experience of fatigue over time in a population of 30 patients with melanoma. The authors collected data on patients' perceptions of causes and their remedies for fatigue and other symptoms at five time points during treatment with subcutaneous interferon alpha. Overall, 36% of patients reported psychological causes, such as depression or worrying, as primary in causing their fatigue. Distraction (40%) and conserving energy (36%) were the two highest responses for fatigue remedies. When describing their fatigue, the patients used 19 items of the Piper Fatigue Scale (PFS) that covered all subscale dimensions: affective, sensory, severity, and temporal. Fu, Anderson, McDaniel, and Armer (2002) used the PFS to measure the fatigue experience of 12 patients with melanoma. Moderate to severe fatigue was reported, with women reporting more intense fatigue.

One intervention study reported the use of exercise and methylphenidate in a sample of 12 patients with melanoma receiving biochemotherapy (Schwartz, Thompson, & Masood, 2002). The results showed that fatigue levels were lower for the exercise and methylphenidate group than historic controls. Functional ability increased with exercise in all patients. Cognitive function was stable for the exercise and methylphenidate group. The exercise-only group showed marked cognitive slowing. The combination of aerobic exercise and methylphenidate may have a positive effect on fatigue, cognitive function, and functional ability. Although this type of intervention requires further testing, evidence suggests that exercise and methylphenidate may provide a practical intervention for practice.

The study reported in this article was designed to describe the problem of fatigue in patients with melanoma who were receiving or had received biotherapy agents in relation to the existing theoretical understanding of fatigue. To guide the choice of factors to measure in the study, the authors used Winningham's psychobiologic entropy hypothesis, which links fatigue with activity, symptoms (physical, psychological, and social), disease and treatment factors, and functional status. The model originally was based on clinical observation that individuals who become less active as a result of disease- and treatment-related symptoms lose "energizing metabolic resources" (Winningham, 1992). According to Winningham's hypothesis, fatigue fulfills a unique and substantial role in the origin of disability that sets it apart from other symptoms. Decreased physical activity, regardless of the cause, leads to decreased capacity for activity. This, in turn, is responsible for increasing fatigue, further decreasing activity, and subsequently resulting in functional disability (see Figure 1).

The purpose of this research was to test Winningham's (1992) hypothesis in the context of biochemotherapy. The specific aims of this study were to describe the variables associated with fatigue as hypothesized by Winningham and to test the relationships among fatigue and activity levels, functional status, nutrient intake, symptoms associated with cancer and cancer treatment, depression, anxiety, and quality of life (QOL).

Methods

The study had a cross-sectional, descriptive design to describe factors hypothesized to be associated with fatigue in two groups of patients receiving biotherapy or biochemotherapy—those currently receiving treatment (on-treatment group) and those who had completed treatment 6–12 months prior (off-treatment group). Questionnaires were administered on one occasion during a routine visit to the medical oncology outpatient clinic. At the same time, weight and height measurements were taken, along with a record of detailed dietary intake. Blood test results (hemoglobin and serum magnesium) from samples taken routinely for clinic visits were accessed through medical records. Permission to conduct the study was obtained from the Health Sciences Institutional Review Board at the University of Missouri–Columbia.

Sample

Men and women older than 18 receiving care for melanoma at the outpatient medical oncology unit at a midwestern cancer center were included in the sample. Additional inclusion criteria for the on-treatment group were that the patients currently were receiving biochemotherapy and had completed at least two cycles of treatment. For the off-treatment group, the additional criterion was that they had completed a course of biochemotherapy 6–12 months prior to data collection.

Measures and Instruments

The measurement and exploration of the variables of interest were considered carefully to minimize, when possible, the burden associated with completing multiple questionnaires. Thus, the shortest, least-tiring instruments available with adequate psychometric properties were chosen to avoid potential loss or exclusion of the most fatigued subjects. Also for this reason, the researchers read the questions to participants who preferred not to read and write.

Fatigue: The **Schwartz Cancer Fatigue Scale (SCFS)** was developed specifically to measure cancer-related fatigue. It is a reliable, valid, parsimonious, six-item instrument that measures fatigue in physical and perceptual dimensions. Psychometric testing originally was conducted on 303 patients with cancer. Scale development included testing content validity, internal consistency, reliability, sensitivity, and construct validity. The scale was able to discriminate between patients on treatment and those who had completed treatment and among groups by the amount of fatigue being experienced currently (Schwartz, 1998). Further instrument development took place with a sample of 212 patients receiving chemotherapy or radiation therapy. Test-retest reliability was established, along with further support for internal consistency.

Activity and functional status: The positive impact of fitness on patients' QOL and their ability to cope physically and emotionally with treatment is a steadily growing body of empirical evidence (Courneya & Friedenreich, 1997, 1999). A simple but trusted method of assessing exercise behavior is the two-item **Leisure Time Exercise Questionnaire** developed by Godin and Shephard (1985). The measure has good concurrent and predictive validity and test-retest reliability (Godin & Bouillon, 1986; Godin & Shephard).

The **Karnofsky Performance Status Scale** (Karnofsky, Abelmann, Craver, & Burchenal, 1948) is used widely for quantifying the physical functioning of patients with cancer and is considered the gold standard by many investigators (Kaasa, Loomis, Gillis, Bruera, & Hanson, 1997). The tool has 11 levels, ranging from normal function (100) to dead (0), and is administered by a physician or nurse. Poor functioning

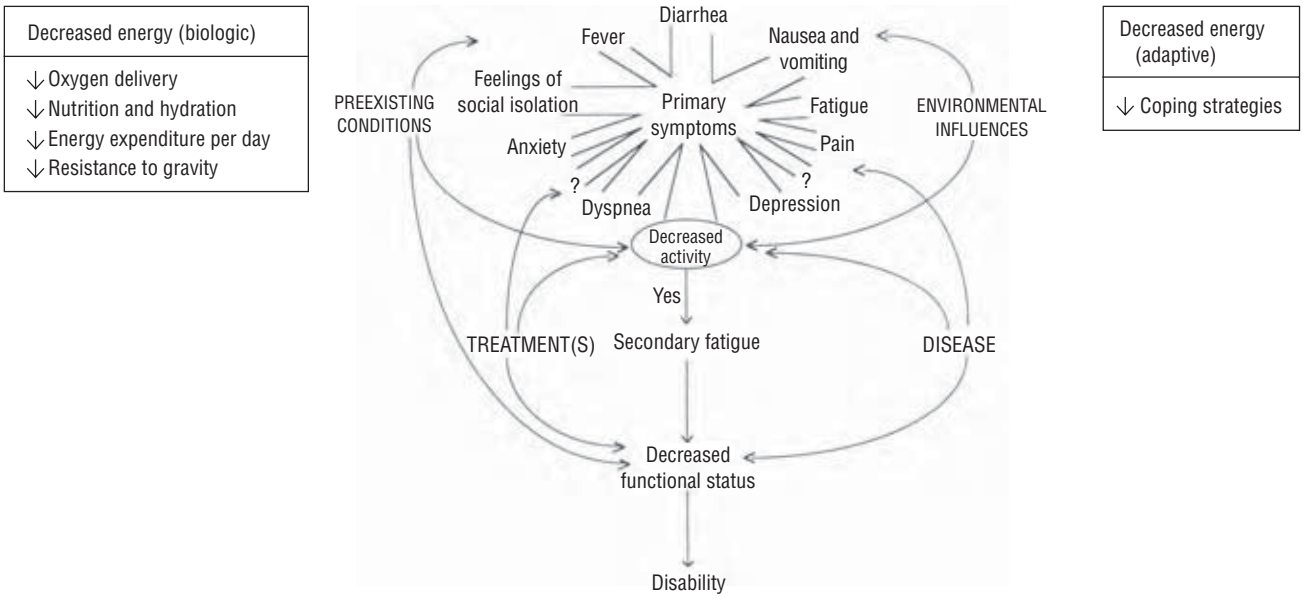

Figure 1. Winningham's Psychobiologic Entropy Hypothesis

Note. From "Fatigue and the Cancer Experience: The State of the Knowledge," by M.L. Winningham et al., 1994, *Oncology Nursing Forum, 21,* p. 25. Copyright 1994 by M.L. Winningham. Adapted with permission.

is associated with increased disease severity (Grieco & Long, 1984) and reduced survival time (Orr & Aisner, 1986).

Cancer and cancer treatment-related symptoms: The relationship between fatigue and other symptoms is hypothesized in Winningham's (1992) framework. These important covariates were measured using the **Adapted Symptom Distress Scale (ASDS) Form 2** (Rhodes, McDaniel, Homan, Johnson, & Madsen, 2000), a 31-item, 5-point, self-report instrument measuring 14 symptoms. These symptoms fit well with the reported symptoms of biotherapy.

Participants were asked to rate each item in terms that best described how they felt during the previous week. The total symptom experience was calculated by summing patient responses to the 31 items. Two subscales, symptom occurrence and symptom distress, also are derived from the scale by summing the items relating to each of these concepts.

Anxiety and depression: Fatigue is acknowledged to be related to negative emotions, in particular depression. Anxiety and depression were measured using the **Hospital Anxiety and Depression Scale (HADS)** (Zigmond & Snaith, 1983). The HADS is a 14-item, self-report questionnaire developed to assess anxiety and depression for use in nonpsychiatric hospital settings. A major advantage over many other depression scales is that it has no items referring directly to feelings of tiredness or sleepiness, which most likely would contaminate the relationship with a fatigue questionnaire. Two subscores are produced, one for anxiety and one for depression. A cutoff score of 8 indicates the need for further investigation for anxiety or depression, and a score of 11 or more indicates clinical anxiety or depression.

Nutritional intake and status: Patients recalled their diets for the 24 hours prior to data collection. The "gold standard" for diet recall has been seven days. However, convincing evidence now shows that a one-day recall reveals very similar findings to seven-day recall, that people are not accurate in recalling what they have eaten beyond four days, and that a seven-day recall can be burdensome (Bingham et al., 1994).

The **24-hour diet recall** was entered into the Diet Analysis software program (Whitney, Cataldo, & Rolfes, 2002). The program's nutrient database was compiled from a variety of sources, including the U.S. Department of Agriculture Standard Release database, literature sources, and manufacturer data. Nutrient data can be viewed only as an approximation of intake because of the variables involved in analyzing food, including the way food is prepared, stored, or processed. The daily recommended intake values used for analysis were taken from the U.S. Food and Drug Administration standards for healthy individuals. No special recommended nutrient intakes exist for people with cancer or any other illness.

Quality of life: Given the number of instruments already used in this study, the authors considered carefully the practicality of including another complex measure. Graham and Longman's (1987) two-question **QOL Scale** asks patients to rate their current QOL on a scale from 1 (poor) to 10 (excellent) and their degree of satisfaction with their current QOL from 1 (not at all satisfied) to 10 (very satisfied). This measure has been tested in outpatients with cancer, with evidence of reliability (interitem correlation of 0.81 [$p < 0.05$]) and content validity (expert panel).

Results

The final sample was comprised of 25 Caucasian adults with a mean age of 47.5 years (SD = 8.3, range = 30–64 years); 17 (68%) were male, 60% of the sample was married, and the majority (88%) lived with a spouse, significant other, or family members. Most (68%) were employed in some capacity, and 80% had at least a high school diploma. Half of the

participants earned $30,000 or more per year, and all but one were insured or self-funded their health care; the remaining participant was receiving Medicare. All participants had received or currently were receiving biochemotherapy for their cancer treatment. Table 1 indicates their treatment status by stage of disease at the time of data collection. All participants were in a fairly advanced stage of melanoma. Six of the eight women and 13 of the 17 men currently were receiving treatment. The remainder (n = 6) had completed treatment 6–12 months prior to data collection. No difference existed in any of these demographic or disease variables between those on treatment and those who had completed treatment.

The treatment received by participants varied in terms of biotherapeutic and chemotherapeutic agents. The authors' medical oncologist team member rated the intensity of the biochemotherapy for each participant. Table 2 details the treatment received by the whole sample.

The SCFS data from this sample show a clear division between items referring to physical fatigue and those referring to psychological responses (see Table 3). To be used for further analysis, the SCFS uses a total score. The mean total fatigue score for the whole sample was 14.9 (SD = 6.16, range = 7–29). No relationship was found between age and fatigue (Spearman's Rho), nor was a significant difference found between men and women (Mann-Whitney U). However, the mean score for the off-treatment group was 7.73 (SD = 0.58) and for the on-treatment group was 17.16 (SD = 5.29). Mann-Whitney U analysis revealed a statistically significant difference in fatigue scores, with the on-treatment group having significantly higher fatigue severity scores (p = 0.000).

Physical Function and Activity Levels

Physical function was measured using the Karnofsky Physical Function Examination. The mean score for participants on treatment was 82.5 (SD = 11.83) and for those off treatment (n = 16) was 94.2 (SD = 10.2). A Mann-Whitney U test found no significant difference between the two groups (p = 0.054).

Activity levels as measured by Godin and Shephard's (1985) exercise questions reflected a diminishing of activity as recalled from before treatment to the time of data collection (see Table 4). Spearman's Rho analysis of participants' reports of activity before treatment showed no significant relationship between the two study groups (p = 0.237). However, current activity for the on- and off-treatment groups was significantly different (p = 0.030). These differences between the groups suggest that activity levels reduce considerably during treatment but are likely to return somewhat to before-treatment levels after 6–12 months. The higher Karnofsky scores support this reasoning. No differences were found in activity levels based on gender.

Nutritional Intake and Weight Loss

Overall, the sample was overweight, with a mean body mass index (BMI) of 29.6 (SD = 5.69, range = 17.6–42.04). Eleven participants had a BMI greater than 30, indicating obesity. Only two participants were underweight. The mean weight of the sample was 90.2 kg (198.4 lbs) (SD = 29.5 kg [64 lbs], range = 49.5–132.9 kg [108.9–292.38 lbs]). Table 5 details the caloric and nutrient intake in the two groups. No significant differences were found using a t test between the participants on treatment and those off of it. No gender differences existed with regard to the intake of any nutrients except iron (t[16.7] = 2.662, p = 0.017) and magnesium (t[22] = 2.088, p = 0.049); women's intake was lower for both nutrients.

Table 1. Participants by Stage and Completion of Treatment

Treatment Status	Stage III Melanoma	Stage IV Melanoma	Total
Current treatment	12	7	19
Completed treatment	5	1	6

Table 2. Intensity of Biochemotherapy

Biochemotherapy	Frequency	%
Low-dose interferon	5	20
High-dose interferon or outpatient subcutaneous interleukin-2	1	4
Biochemotherapy or high-dose interleukin-2	19	76
Total	25	100

Psychological Symptoms and Symptom Experience

Overall, the severity of anxiety and depression was high in all participants, regardless of whether they were receiving or had completed treatment. Ten participants (40%) scored higher than the first cutoff (score ≥ 8) for anxiety, and 15 (60%) scored 8 or more for depression, indicating the presence of symptoms of anxiety and depression. Furthermore, five participants scored higher than the second cutoff on the anxiety score (≥ 11) for a probable diagnosis of clinical anxiety (20%), and four scored above the second cutoff on the depression score (≥ 11), indicating probable clinical depression (16%). A significant difference existed in the mean scores for both anxiety and depression between the on- and off-treatment groups. Table 6 details the anxiety and depression scores and the t test results. Spearman's Rho analysis found a significant relationship between fatigue and anxiety (r = 0.444, p = 0.026) and between fatigue and depression (r = 0.649, p = 0.000). No significant differences existed in the severity of anxiety or depression between men and women.

The ASDS symptom occurrence and distress scores were significantly higher in the on-treatment group. Table 6 details the scores and t test results for all aspects of the ASDS. No significant differences were found in symptom scores between men and women, but a significant positive relationship existed between the total symptoms score and the two subscores of the ASDS and fatigue.

Quality of Life

The mean score for participants' rating of QOL was 5.84 (SD = 2.13, range = 3–10). The mean score for participants' satisfaction with their QOL was 5.56 (SD = 2.48, range = 1–10). Moderately strong significant inverse relationships existed with the total fatigue score for both rating of QOL (r = –0.596, p = 0.002) and satisfaction with QOL (r = –0.632, p = 0.001). Similarly, moderate to strong significant inverse relationships were found between rating and satisfaction with QOL and the depression and anxiety scores, and with the symptom experience scores and current activity levels (see Table 7). Moreover, a significant difference was found between the on- and off-treatment groups in terms of rating of QOL (t[23] = 3.841, p = 0.001) and satisfaction with QOL (t[23] = 3.997, p = 0.001), with higher ratings for those who had completed treatment.

Table 3. Responses to Items on the Schwartz Cancer Fatigue Scale

Schwartz Cancer Fatigue Scale Item	Off Treatment (n = 6)	On Treatment (n = 19)	Total (N = 25)
I feel tired.			
Not at all	–	–	–
A little	5	2	7
Moderately	1	8	9
Quite a bit	–	5	5
Extremely	–	4	4
I have difficulty thinking.			
Not at all	–	5	5
A little	6	6	12
Moderately	–	5	5
Quite a bit	–	1	1
Extremely	–	2	2
I feel overcome.			
Not at all	6	3	9
A little	–	7	7
Moderately	–	4	4
Quite a bit	–	3	3
Extremely	–	2	2
I feel listless.			
Not at all	6	3	9
A little	–	8	8
Moderately	–	3	3
Quite a bit	–	4	4
Extremely	–	1	1
I feel worn out.			
Not at all	3	–	3
A little	3	4	7
Moderately	–	5	5
Quite a bit	–	5	5
Extremely	–	5	5
I feel helpless.			
Not at all	6	6	12
A little	–	5	5
Moderately	–	4	4
Quite a bit	–	4	4
Extremely	–	–	–

Post-Hoc Analysis

Data were collected on the medications that participants were taking. Although this was not a principal factor in the design of the study, the impact of medications on fatigue is a feature of Winningham's (1992) theoretical propositions on factors contributing to fatigue. Sedatives or opiates were being taken by 5 of the 25 participants. Five participants were taking antidepressants, one was using an antidepressant to assist with quitting smoking, and another had a history of depression. Unfortunately, the participants scoring more than 11 on the HADS were not the ones prescribed antidepressants. No difference in fatigue scores was found between those taking or not taking antidepressants, sedatives, or opiates. Furthermore, 10 participants were taking various medications for cardiac problems. The numbers of specific medication types were too small to analyze, but given that a known side effect of beta blockers is fatigue, this is an area for future research and consideration in clinical assessment. The number of medications being taken is a crude estimate of the symptom burden associated not only with biotherapy but also with other chronic conditions. Most participants were taking at least one medication; however, the range was zero to seven. The number of medications taken was significantly correlated with the total fatigue score ($r = 0.49$, $p = 0.012$).

Discussion

The authors' aim was to determine the relationships among physiologic, psychological, and nutritional variables and fatigue in patients with melanoma who had received biochemotherapy. The study revealed several findings that will be of use in developing theory in this area. The limitations of measurement and sample are of particular importance in discussing the findings. First of all, the authors did not get the responses to the SCFS that they expected. The disparity between the severity of physical and emotional responses to fatigue were virtually dichotomous. For example, a participant would rate "tired" at its highest score but "helpless" at the lowest. The sample seemingly did not attribute "helpless, overcome, and listless" with the same severity as "tired, worn out, and difficulty thinking." Terms such as "helpless and overcome" may have deeper meaning about the idea of giving up and not being able to care for yourself that this sample could not or would not report. The authors conducted qualitative interviews with 11 of the participants (Porock & Juenger, 2004), and the main theme of the analysis was "just go with the flow." This describes how patients were feeling totally overwhelmed with fatigue, but to get through treatment, they felt they should put up with it and "just go with the flow." When the authors discussed this finding with colleagues, many suggested that the inability to select "helpless and overcome" on the questionnaire was related to "midwestern stoicism." The disparity between the interview responses and the questionnaire responses is interesting. However, in terms of quantitative measurement of fatigue, the disparity calls into question the validity of the measure.

This sample of patients also had some characteristics of unknown representativeness. The sample predominantly was overweight, and a substantial proportion was obese. Their caloric intake generally was high and probably explains the level

Table 4. Activity Levels Before Treatment and at Data Collection

	Off Treatment		On Treatment	
Activity Level	Before Treatment	At Data Collection	Before Treatment	At Data Collection
How often did you take part in active sports or vigorous physical activity long enough to get sweaty?				
• Not at all	–	1	4	11
• Less than once per month	–	–	1	2
• About once per month	3	2	2	1
• About two or three times per month	–	1	3	2
• About one or two times per week	–	1	3	2
• About three or more times per week	3	1	6	1
Total participants	6	6	19	19

Table 5. Mean Calorie and Nutrient Intake and Percent of Daily Recommended Intake (DRI)

Nutrient	Off Treatment $\bar{X}$ (SD) Intake	Off Treatment % of DRI (SD)	On Treatment $\bar{X}$ (SD) Intake	On Treatment % of DRI (SD)	Nutritional Intake t	% of DRI t
Calories (kcals)	2,164.12 (932.54)	82.83 (37.48)	1,938.64 (886.92)	73.11 (31.85)	0.533	0.519
Protein (g)	83.40 (47.33)	106.83 (65.73)	93.45 (65.50)	117.11 (84.06)	−0.345	−0.272
Carbohydrates	274.40 (93.47)	72.17 (24.41)	199.78 (68.50)	52.33 (19.05)	2.113	2.063
Fat	81.66 (51.55)	95.00 (63.84)	86.60 (57.73)	98.33 (61.77)	−0.186	−0.114
Vitamin A	493.25 (301.56)	51.67 (28.83)	711.34 (698.08)	75.22 (71.07)	−0.734	−0.781
Vitamin B_{12}	4.11 (4.80)	171.33 (199.86)	4.69 (4.25)	195.33 (177.35)	−0.278	−0.279
Folate	376.68 (360.27)	94.17 (90.18)	202.31 (106.48)	50.56 (26.74)	1.169	1.168
Vitamin C	146.06 (132.43)	172.50 (147.40)	70.19 (66.18)	82.89 (82.33)	1.875	1.884
Iron	16.55 (13.24)	153.50 (139.56)	12.63 (7.31)	123.00 (75.43)	0.923	0.689
Magnesium	235.04 (137.73)	61.33 (32.92)	196.68 (96.34)	50.06 (22.03)	0.760	0.960
Zinc	10.53 (13.33)	74.00 (88.13)	8.46 (7.04)	59.56 (46.76)	0.494	0.521

of obesity. No relationship was established between fatigue and caloric intake or specific nutrients such as protein, carbohydrates, or fat. This is contrary to current theories about fatigue that suggest that energy taken in is related highly to level of fatigue (Piper et al., 1987; Winningham, 1992). Why did these findings not corroborate that hypothesis? The authors' first thought was that the problem already identified with the fatigue scale resulted in scores of moderate fatigue with little variation in scores. This made it difficult to find a relationship between nutritional intake and fatigue when that, too, was a variable with little variation in the sample. This leads the authors to speculate that when a patient population is eating sufficient (or more than sufficient) calories, the relationship between dietary intake and fatigue is not relevant. Nutrition could be more important in relationship to fatigue when the intake is depleted and a patient is underweight.

Activity levels, an important contributing factor of fatigue in Winningham's (1992) theory (see Figure 1), were found to be significantly different for those on and off treatment. Previous findings also have suggested that the adverse effects of therapy are reversible given time after treatment (Kirkwood et al., 2002). The findings suggest that a considerable reduction in activity occurs during treatment. According to Winningham's theory, this is a serious problem because inactivity leads to a cyclical deconditioning effect that exacerbates fatigue and leads to further inactivity. The question to be asked, therefore, is whether a physical activity intervention with this population would reduce the decline in activity during treatment and reduce overall fatigue during treatment. Informing prospective patients that some evidence suggests that physical activity levels return 6–12 months later gives some encouragement for those coping with this problem during treatment.

Psychological symptoms measured by anxiety and depression in this study indicated a high prevalence of distress. The post-hoc analysis also revealed that those identified as having severe symptoms of depression were not the ones being treated with antidepressant therapy. Depression as an adverse effect of biotherapy has been noted before in the medical literature (Kirkwood et al., 2002). Given the strong relationship between depression and fatigue, depression must be given more attention, particularly in patients receiving biotherapy.

Winnningham's (1992) theory provided a basis for the understanding of fatigue in patients receiving biochemotherapy for melanoma. The theory is the most sophisticated of the current theories proposed in the literature, but some serious issues of measurement need to be addressed. For example, no measurement methodology has been developed for testing Winningham's theory, nor have instruments been designed specifically for that purpose. This study attempted to bring several measures together that reflected various aspects of the theory, but the respondent burden is great, and a more pragmatic method needs to be developed.

Table 6. Symptom Scores, Anxiety, and Depression

Symptom Score	$\bar{X}$ (SD)	t (df)	p
Anxiety score		−2.802 (23.00)	0.010
Off treatment	10.50 (1.52)		
On treatment	15.10 (3.88)		
Depression score		−4.915 (23.00)	0.000
Off treatment	9.50 (2.07)		
On treatment	15.95 (2.97)		
Symptom occurrence		−4.554 (18.78)	0.004
Off treatment	8.00 (3.35)		
On treatment	17.68 (7.10)		
Symptom distress		−3.618 (23.00)	0.001
Off treatment	6.33 (4.42)		
On treatment	17.37 (6.98)		
Symptom experience		−3.576 (23.00)	0.002
Off treatment	14.33 (3.04)		
On treatment	35.05 (13.42)		

Table 7. Relationships Among Fatigue, Anxiety, Depression, Distressing Symptoms, and Activity Levels

Test Variable	R-Coefficient for Rating of QOL	p	R-Coefficient for Satisfaction With QOL	p
Total fatigue score	−0.596	0.002	−0.632	0.001
Anxiety score	−0.589	0.002	−0.594	0.002
Depression score	−0.758	< 0.001	−0.630	0.001
Symptom experience	−0.723	< 0.001	−0.703	< 0.001
Symptom occurrence	−0.681	< 0.001	−0.656	< 0.001
Symptom distress	−0.719	< 0.001	−0.704	< 0.001
Activity before treatment	0.296	0.151	0.268	0.196
Activity at data collection	0.403	0.043	0.421	0.036

QOL—quality of life

In conclusion, this study showed only moderate overall fatigue in a sample of patients with melanoma who were receiving or who had received biochemotherapy. Fatigue was higher in the on-treatment group than for those who had completed treatment 6–12 months earlier. Activity levels probably return to close to pretreatment levels after 6–12 months. The nutrient intake of the patients has been reported in this article in some detail. The literature reports very little about what patients with cancer eat, so this is a small contribution to that knowledge. Based on the current study, little can be determined about the effect of nutrients on fatigue in an overweight or obese sample. Depression is a significant factor in this population and needs to be assessed systematically and treated as a recognized toxicity of biochemotherapy.

Winningham's (1992) model demonstrates its usefulness in helping to understand the phenomenon of cancer-related fatigue. The need to have better measures of fatigue is well illustrated by this study and should be a focus of future research.

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