Cancer-Related Fatigue and Its Associations With Depression and Anxiety: A Systematic Review

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Background: *Fatigue is an important symptom in cancer and has been shown to be associated with psychological distress.* **Objective:** *This review assesses evidence regarding associations of cancer-related fatigue with depression and anxiety.* **Method:** *Database searches yielded 59 studies reporting correlation coefficients or odds ratios.* **Results:** *The combined sample size was 12,103. Almost all studies showed a correlation of fatigue with depression and with anxiety. However, 31 different instruments were used to assess fatigue, suggesting a lack of consensus on measurement.* **Conclusion:** *This review confirms the association of fatigue with depression and anxiety. Directionality needs to be better delineated in longitudinal studies.*

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Fatigue is a pervasive and vexing problem in individuals with cancer. It adds considerably to suffering and exists across all types and stages of the disease. It has been found to be a problem before, during, and after treatment, sometimes continuing long after treatment has ended, even in those believed to be disease-free.[1] Cancer-related fatigue (CRF) has been reported by up to 40% of patients at diagnosis, 90% of patients treated with radiation, and 80% of those under chemotherapy treatment.[1] Research has found that in patients with advanced cancer, fatigue is one of the most common and disabling symptoms.[2–5] In view of its prevalence and detrimental impact on quality of life, fatigue is an important symptom to target in the treatment of cancer survivors.

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NEW FOCUS ON UNDERSTANDING CANCER-RELATED FATIGUE

The mechanisms of CRF are not well understood, but it is known to occur both as a consequence of the cancer itself and as a side effect of treatment.[1] Until recently, CRF was infrequently discussed or treated, partly because of focus on other symptoms, such as pain, nausea, and vomiting, and partly because fatigue was considered an unavoidable symptom, to be endured rather than treated.[2] Fortunately, fatigue has recently caught the attention of cancer researchers who are seeking to better understand its nature in order to develop effective interventions. A recent state-of-the-science statement from the National Institute of Health (NIH) called for more efforts toward symptom-management in cancer, with fatigue named specifically, along with pain and depression, as the symptoms needing attention.[6] Based on a panel's evaluation of available evidence, the report called for prospective research focused on the definition, occurrence, assessment, and treatment of these three cancer symptoms and their interrelationships.

Two of the three symptoms in the NIH call to action—fatigue and depression—are a focus of this review, along with anxiety. Their interrelationships in cancer patients are of special interest. Psychological symptoms, especially depression and, to a lesser degree, anxiety, have been found to have relatively high correlations with CRF. In fact, depression's relationship to fatigue has been shown to be of greater magnitude than that of disease activity as measured by such markers as nutritional status and tumor-specific tests.[7] Understanding the nature of these relationships, however, has proven elusive. Does a cancer patient become depressed and/or anxious because of the effects of being fatigued or might it be the reverse? Alternatively, is there a bidirectional relationship between the two symptoms, with each having an influence on the other? Are there external factors that independently cause both fatigue and depression and/or anxiety? Also, does the relationship of CRF with depression and anxiety differ by type and stage of cancer, by type of cancer treatment, or by differences within the person?

Measurement Issues

Measurement is an important issue, particularly, the ability to distinguish fatigue from depression. Both fatigue and depression are heterogeneous constructs, with physical, cognitive, and emotional dimensions and a high degree of overlap across the dimensions. For example, "fatigue or loss of energy nearly every day" is one of the core symptoms used in establishing a clinical diagnosis of depression.[8] Both constructs can be assessed as a single symptom, a cluster of symptoms, or a clinical syndrome.[9] Both are measured primarily by self-report. Cancer patients often endorse items that could be interpreted as suggesting high levels of fatigue, high levels of depression, or both. A recent review found 26 different scales that had been used to assess CRF, some of which were developed specifically for cancer fatigue and some of which were not specific to cancer.[10]

The discriminant validity of the existing measures has been called into question by the generally high positive correlations found on continuous measures of fatigue and depression administered together.[11] However, some studies have found that the correlation of fatigue and depression remains high even after removing the fatigue items from depression measures.[12–14] Furthermore, fatigue measures correlate rather strongly with measures that assess just the mood aspects of depression.[15] Some have suggested that the overlap problem may be addressed by use of a single-item measure in which patients are asked to rate fatigue experience on a 1-to-10 scale, such as "to what degree have you experienced fatigue during the past week?"[10] Others have proposed that CRF is best measured as a syndrome, using a set of diagnostic criteria. Such a set has been proposed for future inclusion in the International Classification of Diseases 10th Edition. To meet criteria, a cancer survivor must experience at least 6 of 11 symptoms and meet three other requirements, one of which is that the symptoms are not related to a comorbid condition, such as major depression.[16] Because measurement issues may confound attempts to understand the relationship between CRF and psychological variables, we include it as a secondary topic in this review.

Purposes of the Present Review

In undertaking this review, we expected to find a recent increase in the number of studies examining associations between CRF and depression and anxiety, and we expected to find consistently significant correlations. Although the association between CRF and depression has been previously reviewed,[15,17–19] our current review provides several important contributions to the literature. First, the inclusion of new studies substantially expands the number of studies evaluated. Second, it is the first systematic review of studies reporting associations between CRF and anxiety. Third, special attention is directed to methods of measurement in the effort to distinguish CRF from depression. Fourth, longitudinal studies are highlighted in order to explore potential causal relationships between CRF, depression, and anxiety.

METHOD

Literature Search and Study Selection

We searched MEDLINE and PsychInfo databases, using keywords or descriptors "fatigue" and "cancer" or "neoplasms" and "anxiety" or "depression." The search was limited to English-language journal articles or chapters. No date limits were imposed; the MEDLINE database included articles from 1950 to 2007, and PsychInfo covered from 1806 to 2007. These searches yielded 160 "hits" in MEDLINE and 113 in PyschInfo. Each abstract was reviewed, and articles were considered for inclusion if the cancer sample size was at least 25, provided that fatigue was mentioned as a primary outcome in either the title or the abstract. The selected articles were further reviewed to identify those that provided correlation or odds ratio sta-

tistics for fatigue and its association with depression, anxiety, or both. All original research articles that met these criteria were included. Articles were added that did not result from the database search but were located by reviewing reference lists of retrieved articles.

Data were abstracted on the following key variables: sample size; type and stage of cancer; control group, if there was one; treatment status; and specific measures of fatigue, depression, and anxiety used. The correlation of fatigue with depression and/or anxiety was the primary outcome extracted from each article.

Data Analysis

Average untransformed correlation coefficients, weighted by sample size, have been suggested as the preferred summary statistic in reviews of correlational studies.[20] Weighted average correlations of fatigue with depression and with anxiety were computed by multiplying the sample size by the appropriate correlation coefficient for each study and dividing the sum of the products of all studies by the total sample size across all studies. For longitudinal studies reporting correlations at multiple time-points, the average of the reported correlation coefficients was entered into the analysis. Confidence intervals (95% CI) were calculated by use of Fisher's z transformation. Coefficients of determination were calculated for the summary statistics. A calculation of r^2 provides the coefficient of determination, which suggests the proportion of variance in a construct that is accounted for by its associated variable. Average odds ratios (OR), weighted by sample size, were calculated separately.

RESULTS

Fifty-nine research articles were ultimately included,[4,5,12–14,21–74] the earliest of which was published in 1989. The majority of studies (N=52) have been published in the last decade (1998 to 2007), indicating a marked increase in research interest in fatigue and its association with psychological variables. Fifteen of the studies had scale validation as a primary objective. The individual studies and key findings are presented in an online data supplement (*psy.psychiatryonline.org*).

Study Characteristics

The total number of subjects from all studies was 12,103. Twenty-three of the studies (39%) were longitudinal, and 12 included a control or comparison group, which, in most cases, were individuals with no cancer history. Most studies reported correlation coefficients; five reported odds ratios. Twenty-one studies focused on a breast cancer sample, four on lung cancer patients, four on hematological disease, two on prostate cancer, one on testicular cancer, and four on a mix of specific cancers. The remaining 23 studies included patients with any cancer type. Studies in which treatment status was specified most commonly focused on the posttreatment period (13 studies). Ten studies included only participants who were disease-free after treatment, and three looked at patients characterized as "long-term survivors," ranging from at least 1 year post-diagnosis to 10 years-and-beyond. Six studies focused on advanced cancer patients, and three on persons in palliative care. Study attributes are presented in Table 1.

Fatigue and Depression

Depression was significantly associated with fatigue in every study in which the correlation was reported except one, and in some cases the magnitude was strong. The range of correlation coefficients was 0.16 to 0.84. The average correlation between fatigue and depression, weighted by sample size, was 0.56 (95% CI: 0.54–0.58)

TABLE 1. Characteristics of Study Samples

	Number of Studies
Cancer type/site	
Breast cancer	21
Lung cancer	4
Hematological	4
Prostate	2
Testicular	1
Mix of specific types	4
Any cancer type	23
Disease status	
Disease-free after treatment	10
Advanced cancer	6
Long-term survivorship	3
Type or stage of treatment	
Post-treatment	13
Receiving chemotherapy	7
Receiving radiotherapy	6
Bone marrow/stem-cell transplant	4
Receiving palliative care	3
Currently receiving either chemotherapy or radiotherapy	2
Currently receiving hormone therapy	1
Currently receiving treatment, type not specified	3

across the 51 studies reporting this statistic (Table 2). The unweighted average was 0.57. A calculation of the coefficient of determination (r^2) suggests that fatigue shared approximately 31% of its variance with depression. It should be noted that 31 different scales were used to measure fatigue, potentially contributing to some of the variation across studies. For the three studies reporting odds ratios, the weighted average association of fatigue with depression was 1.16.

Fatigue and Anxiety

Anxiety was significantly correlated with fatigue in 33 of the 35 studies reporting the association, although the magnitude was not as great as for depression. The range of correlation coefficients was 0.16 to 0.73. The weighted average was 0.46 (95% CI: 0.44–0.49), and the unweighted average was 0.49. The coefficient of determination, weighted by sample size, indicated that fatigue shared about 23% of its variance with anxiety across all the studies. The weighted mean for the two studies reporting odds ratios was 1.19.

Measurement Issues

A lack of consensus about the best way to measure fatigue in cancer research is demonstrated by the fact that 31 different instruments were used to assess fatigue in the 59 studies. No single scale emerged as a clear favorite. The instrument used most frequently, the Multidimensional Fatigue Inventory, was used in only 9 of the 59 studies. In contrast, two scales predominated for measuring depression: a subscale of the Hospital Anxiety and Depression Scale (HADS)[75] was used in 24 studies, and the Center for Epidemiological Studies–Depression Scale (CES–D)[76] was used in 14. In all, 12 depression scales were used across all studies. The HADS was also the favored instrument to measure anxiety, serving that purpose in 21 studies. Six different scales for anxiety were used across all studies. Table 3 provides details about the measures used in the 59 reviewed studies. Further information about most CRF scales, including reliability and validity data, can be found in a review by Wu and McSweeney.[77]

A few investigators took steps to reduce potential measurement overlap in order to enhance discrimination between fatigue and depression. For example, two groups

TABLE 2. Mean Associations With Cancer-Related Fatigue (CRF) Across Studies, Weighted by Sample Size

	Correlation Coefficients	95% Confidence Intervals	Odds Ratios
Depression	0.56	0.54 – 0.58	1.16
	N=7,508		N=4,027
Anxiety	0.46	0.43 – 0.49	1.19
	N=4,710		N=1,150

TABLE 3. Measurement Scales Used

Measure	Number of Studies
Fatigue	
Multidimensional Fatigue Inventory	9
Functional Assessment of Cancer Therapy, Fatigue subscale	6
Profile of Mood States, Fatigue/Inertia subscale	7
Fatigue Symptom Inventory	5
Visual-Analog Scale, 100-meter	5
Cancer Fatigue Scale	5
European Org. for Research and Treatment of Cancer, 30-item QoL scale	4
Fatigue Assessment Questionnaire	3
Fatigue Symptom Inventory	3
Piper Fatigue Scale	3
Short-Form 36 Health Status Survey	3
Bi-dimensional Fatigue Scale	2
Fatigue Questionnaire	2
Fatigue Symptom Checklist, 30-item	2
Multidimensional Fatigue Symptom Inventory	2
Multidimensional Assessment of Fatigue	2
Others; each used in single study[a]	14
Depression	
Hospital Anxiety and Depression Scale, Depression subscale	24
Center for Epidemiological Studies, Depression subscale	14
Profile of Mood States, Depression subscale	6
Beck Depression Scale	4
Zung Self-Rating Depression Scale	3
Symptoms Checklist-90	2
Geriatric Depression Scale	2
Others; each used in single study[a]	5
Anxiety	
Hospital Anxiety and Depression Scale, Anxiety subscale	21
Spielberger Trait-Anxiety Inventory	9
Profile of Mood States, Tension/Anxiety scale	3
Symptoms Checklist-90	2
Visual Analog Scale, 100-meter	2
Brief Symptom Inventory	1

[a] Brief Fatigue Inventory, Chalder Fatigue Scale, Checklist Individual Strength, Fatigue Numerical Scale, Lee Fatigue Scale, Linear Analog Self-Assessment, Memorial Symptom Assessment Scale Short Form, Symptom Distress Scale, Symptom Experience Scale, Wu Cancer Fatigue Scale, a customized test for asthenia, a single item from the Zung Self-Rating Depression Scale, a 1-item energy scale, and a structured interview.

of researchers who chose the CES–D described its advantage of focusing on cognitive and affective symptoms of depression, rather than physical symptoms, thus minimizing overlap with fatigue items.[28,53] Visser and Smets[72] dropped six items of the CES–D that measured somatic symptoms to avoid construct overlap in their analysis and nevertheless found significant correlations between fatigue and depression (range of 0.35 to 0.48 across three time-points).

Some felt that an advantage of the HADS is that its depression subscale does not include any physical symptoms such as "lack of energy" or "sleep disturbance," thereby reducing potential contamination of the relationship with a measure of fatigue.[12,38,40] However, Item 8 of the HADS–D, "I feel as if I am slowed down," can be deemed as similar to fatigue and was therefore dropped from the analyses of correlation with fatigue in five studies.[12–14,66,70] Four of these five studies still found significant correlations between fatigue and depression, ranging from 0.46 to 0.70, with only one study showing a nonsignificant relationship.[70]

The Zung Self-Rating Depression scale (SDS) is another instrument that was modified to minimize overlap with fatigue measures. Passik and colleagues[31] used an abbreviated version, in which 9 of 20 items were dropped because the somatic nature of the items could lead to confounding of cancer and its treatment. In another study, 3 of the 20 items were excluded because of concern that the items reflected somatic symptoms of fatigue.[34] Nevertheless, relatively high correlations of fatigue with depression were found. Kirsh and colleagues[56] singled out an item from the SDS: "I get tired for no reason," and tested its utility as a single-item measure of CRF. They found the item to have a relatively high correlation with both the SDS ($r=0.63$) and their fatigue measure ($r = -0.70$).

Longitudinal Studies

The average weighted correlation coefficients of fatigue with depression and anxiety in longitudinal studies were not significantly different from those statistics across all 59 studies. Of the 23 studies that were longitudinal, 15 investigated associations between fatigue and depression or anxiety at multiple time-points. Of these 15 studies, 5 examined patients undergoing radiation therapy; 4 had a sample of patients receiving chemotherapy; 2 were during stem-cell transplant; 1 during hormone therapy; 1 during treatment in leukemia patients; and 2 sampled cancer patients post-treatment. We examined these studies to see whether patterns could be detected relative to the directional relationships between fatigue, depression, and anxiety. Overall, no such pattern emerged, partly because of heterogeneity of the samples between studies and partly because of inconclusive or contradictory findings. In only two studies did the authors clearly assert that their findings suggest that changes in fatigue were associated with changes in depression and anxiety.[13,25] Authors of at least four studies concluded that no evidence of relationships in longitudinal changes had been found; two studies referred to depression only,[68,72] and two assessed both depression and anxiety.[14,50] Authors of the remaining studies reported findings that were relatively ambiguous on this matter.

DISCUSSION

Depression is consistently moderately associated with CRF. Anxiety is also an important correlate, though at a somewhat lower magnitude than depression. Taking into account the complex and multifactorial nature of fatigue, even moderate associations are impressive. These findings support the conclusions of previous reviews of psychological correlates of CRF.[15,17–19] Moreover, our systematic review included 59 studies—nearly double that of the largest previous review (30 studies).[18] The heterogeneity of the 59 studies, however, precludes specific conclusions about the directionality or mechanisms underlying the relationships among fatigue, depression, and anxiety. Furthermore, data on these constructs are inherently subjective and subject to recall bias, further limiting the potential for conclusive inferences.

The consistent correlation between depression and CRF has raised questions about a common etiology. Jacobsen and Weitzner[15] discussed three possible causal relationships: 1) fatigue causes depression in cancer patients; 2) depression causes fatigue in cancer patients; or 3) a third factor may cause both depression and fatigue. Although the authors cited some supporting evidence for each of these possibilities, their findings were inconclusive. Depression is a predisposing factor for the development of chronic fatigue syndrome,[78,79] but CRF may have different mechanisms. Some studies suggest that fatigue and depression are independent conditions in cancer patients, with patterns that differ over the course of disease.[72,78] The subset of longitudinal studies in this review assessing fatigue, depression, and/or anxiety at several time-points provides additional support for an interdependence among these symptoms, although the varied findings still do not provide definitive evidence for whether

fatigue is a consequence of these psychological factors, a cause, or the product of a common pathway. The development of CRF may involve several physiological, biochemical, and psychological systems,[79] which, in turn, may vary by type of cancer, stage of disease, and type of treatment.

Further research with robust measures, administered at multiple time-points, and more sophisticated statistical analyses, such as times-series or structural-equation modeling might be informative. Also, translational research examining biological or physiological measures (e.g., cytokines, neuroimaging) might disclose both shared as well as disparate mechanisms underlying fatigue, depression, and anxiety. Control groups of non-cancer populations (including healthy individuals), individuals with fatigue or depression/anxiety only, or patients with comorbid medical illnesses might further enrich our understanding of the fatigue–depression–anxiety relationship.

Intervention studies aimed at improving outcome variables that are correlated with CRF may also be helpful in teasing apart the interrelationships.[7] For example, an intervention that improves cancer-related depression could be evaluated in terms of its concomitant effect on fatigue. Conversely, interventions targeting fatigue could be analyzed for effects on depression and anxiety. Along those lines, Tchekmedyian and colleagues[25] found that improvements in fatigue in 250 lung cancer patients receiving darbepoetin-alfa for treatment of anemia were associated with parallel reductions in depression and anxiety. In this type of research, it is critical to include elevated fatigue levels as an inclusion criterion.

Fewer studies have explored the relationship between anxiety and CRF and have often done so as an adjunct to investigating depression's associations with CRF. In many studies that included both variables, depression and anxiety scores were reported as if operating as a cluster. A few studies found CRF associations that were specific to anxiety, however, such as the correlation of trait-anxiety with CRF and the effects of baseline anxiety on later fatigue, depression, or anxiety.[38,39,44,49,51,55] Moreover, our pooled results suggest that anxiety is consistently associated with CRF. Thus, anxiety warrants inclusion as an important psychological variable in future CRF research.

The measurement challenges described demand careful attention in future studies. It has been problematic that such a wide variety of measures have been used to measure fatigue. Research in this domain will benefit if the field of fatigue instruments is narrowed to a few that have been well-validated, so as to accurately assess CRF and distinguish it from depression. Latent-variable path analysis may be particularly useful in future research. In longitudinal studies, this structural-equation modeling technique can support or disconfirm a priori hypotheses about directionality of causal effects. The procedure may reduce effects of measurement error by assessing multiple indicators of study constructs within a single analysis.[80]

In conclusion, cancer-related fatigue (CRF) is an important and highly prevalent symptom that negatively affects cancer patients' quality of life and therefore should be a high priority for treatment. Depression and anxiety are prominent among the correlates of CRF; however, the nature, as well as the direction of causality, among these variables remains uncertain, despite a recent increase in research interest in this area. More longitudinal and/or intervention studies would be desirable, as well as more uniform measures across multiple studies. Meanwhile, clinicians should screen for and treat the comorbid depression and anxiety that commonly accompany cancer-related fatigue.

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