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By Linda F. Brown

Entitled Depression and Cancer-Related Fatigue: A Cross-Lagged Panel Analysis of Causal Effects

For the degree of Doctor of Philosophy

Is approved by the final examining committee:

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DEPRESSION AND CANCER-RELATED FATIGUE:

A CROSS-LAGGED PANEL ANALYSIS OF CAUSAL EFFECTS

A Dissertation

Submitted to the Faculty

of

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by

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ABSTRACT

Brown, Linda F., Ph.D., Purdue University, August 2011. Depression and Cancer-Related Fatigue: A Cross-Lagged Panel Analysis of Causal Effects. Major Professor: Silvia M. Bigatti.

Fatigue is one of the most common and debilitating symptoms reported by cancer patients, yet it is infrequently diagnosed or treated. Relatively little is understood about its etiology in the cancer context. Recently, as researchers have begun to focus attention on cancer-related fatigue (CRF), depression has emerged as its strongest correlate. Few longitudinal studies have been done, however, to determine whether causal influences between the two symptoms exist. The aim of the current study was to determine whether depression has a causal influence on CRF and whether reciprocal effects exist. The study used a single-group cohort design of longitudinal data from a randomized controlled trial (N = 405) of an intervention for pain and depression in a heterogeneous sample of cancer patients. To be eligible, participants met criteria for clinically significant pain or depression. A hypothesis that depression would influence change in fatigue after 3 months was tested using latent variable cross-lagged panel analysis, a structural equation modeling technique. A second hypothesis was that fatigue would also influence change in depression over time but at a lesser magnitude. Depression and fatigue were strongly correlated in the sample (i.e., baseline correlation of latent variables was 0.72). Although the model showed good fit to the data, χ^2 (66, N = 329) = 88.16, p = 0.04, SRMR = 0.030, RMSEA = 0.032, and CFI = 1, neither cross-lagged structural path was significant. The findings suggest that depression had no causal influence on changes in fatigue in this sample, and fatigue did not influence change in depression. The clinical implication is that depression treatment may not be helpful as a treatment for CRF and therefore

interventions specifically targeting fatigue may be needed. Future research should include additional waves of data and larger sample sizes.

INTRODUCTION

Fatigue is a vexing problem in individuals with cancer. It is the most common symptom reported by cancer patients (Berger et al., 2009), 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 free of disease (Hofman, Ryan, Figueroa-Moseley, Jean-Pierre, & Morrow, 2007). Cancer-related fatigue (CRF) has been reported by up to 40% of patients at diagnosis, by 90% of patients receiving radiation treatment, and 80% of those undergoing chemotherapy (Hofman et al., 2007). Cancer patients' experience of fatigue has been found to be significantly higher than healthy comparison groups with no cancer history, both during treatment and after it has ended (Prue, Rankin, Allen, Gracey, & Cramp, 2006). In research in patients with advanced cancer, fatigue is one of the most common and disabling symptoms (Chan, Richardson, & Richardson, 2005; Curt et al., 2000; Higginson, Armes, & Krishnasamy, 2004; Respini, Jacobsen, Thors, Tralongo, & Balducci, 2003). In view of its prevalence and detrimental impact on quality of life, CRF is an important symptom to target in treatment.

BACKGROUND

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 (Higginson et al., 2004). Advances in cancer treatments have resulted in greater numbers of survivors who live many years beyond the end of treatment (Valentine & Meyers, 2001) and as a result, more attention must be directed to the quality of life of survivors and the associated effects of symptoms such as fatigue. Fortunately, fatigue has recently caught the attention of cancer researchers 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 (Patrick et al., 2002). Based on a panel's evaluation of available evidence, the report called for adequately funded prospective research focused on the definition, occurrence, assessment, and treatment of these symptoms and their interrelationships.

The current study focuses on interrelationships between two of the three symptoms in the NIH call to action—fatigue and depression. Psychological symptoms have been found to have strong associations with CRF. In fact, depression's relationship to fatigue has been shown to be even stronger than that of disease activity as measured by such markers as nutritional status and tumor-specific tests (Hotopf, 2004). Understanding the nature of this relationship, however, has proven elusive. Does a cancer patient become depressed because of the effects of being fatigued or might it be the reverse? Might there be bidirectional influences? Are there external factors that independently cause *both* fatigue and depression? Research to date has made little progress in teasing the relationships apart. Adding to the challenge is the issue of individual differences.

Besides the differences inherent in each person, each case of CRF carries with it a particular combination of cancer type, stage, type and phase of treatment, and prognosis.

The current study was undertaken to extend the understanding of the relationship of depression and CRF in a way that will inform the development of effective treatment of these symptoms in cancer patients. It is important to know whether reductions in depression lead to decreased CRF, if the reverse might be true, and to what degree effects are bidirectional. A predominant effect in one direction (i.e., depression improvement accounting for much of the improvement in fatigue) might support a "treat depression first" strategy. In contrast, a bidirectional relationship might suggest interventions that either treat fatigue and depression as a cluster (i.e., treatments that have proven effective for both symptoms) or that comprise "dual-diagnosis" treatments (i.e., fatigue-specific therapy coupled with depression-specific therapy).

Cancer-Related Fatigue

Fatigue is not only the most common symptom in cancer patients (Berger et al., 2009), it is also generally acknowledged in the literature as one of the most debilitating of symptoms. In several studies, CRF was rated as more troublesome and detrimental to quality of life (QoL) than other cancer-related symptoms including pain, depression, and nausea (Hofman et al., 2007). Perhaps most troubling is the fact that CRF sometimes persists for months or even years after treatment is completed (Hofman et al., 2007; Prue et al., 2006). It is highly subjective and its etiology is complex and multidimensional (Mustian et al., 2007; Ryan et al., 2007). People with cancer typically experience fatigue differently from those in the general population. In a healthy person, fatigue serves as a signal to rest and is a protection from overexertion, which could lead to injury or illness. It abates after an appropriate period of rest (Ryan et al., 2007). In contrast, CRF is an unpleasant sensation often accompanied by cognitive and emotional distress and frustration. Compared to normal fatigue, it tends to be more intense and severe, of longer duration, and is not relieved by adequate rest (Wu & McSweeney, 2004).

Characteristics and Correlates of CRF

CRF has been defined as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" (Berger et al., 2009, p. FT-1). It is subjectively experienced by some individuals as physical tiredness; others experience it as a need to reduce activity, a reduction in motivation, or a feeling of mental fatigue (Ryan et al., 2007). CRF can adversely affect cognitive function; on the other hand, impaired cognitive function may lead to fatigue (Valentine & Meyers, 2001).

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. In some cases, CRF emerges as an early symptom of the disease; in others it may be a side effect of chemotherapy, radiotherapy (RT), bone marrow transplantation, or biological response modifier treatment (Berger et al., 2008; Hofman et al., 2007). The degree to which fatigue is caused by the cancer itself, its treatments, or interactions of the two is unknown but important (Andrews, Morrow, Hickok, Roscoe, & Stone, 2004). The presence of comorbid conditions such as anemia, cachexia, sleep disorders, and depression can be a complicating factor (Ryan et al., 2007).

Three recent reviews summarized evidence regarding the prevalence, correlates, and patterns of CRF (Lawrence, Kupelnick, Miller, Devine, & Lau, 2004; Prue et al., 2006; Servaes, Verhagen, & Bleijenberg, 2002). Prue and colleagues (2006) reviewed 44 studies that used multidimensional measures of CRF, 32 of which were longitudinal. Lawrence and colleagues (2004) reviewed 27 studies that were relevant to occurrence of CRF, 56 that were relevant to assessment, and 10 randomized controlled trials (RCTs) of interventions for CRF. The reviewers found fatigue's correlation with psychological distress—depression in particular—to be a "common theme" in several studies. In a review of 54 studies, Servaes and colleagues (2002) found that most studies of CRF focused on its association with depression. A summary of key findings of the reviews is presented at Appendix A. All three reviews concluded that CRF is correlated with depression and anxiety, as well as other symptoms such as sleep disruption, pain, and

shortness of breath. Findings were mixed and unclear as to CRF's association with biological markers and disease and treatment factors. The majority of studies reviewed found no relationship between fatigue and demographic variables. Two of the reviews reported finding a few studies supporting age and gender relationships, and the other review concluded there is no relationship.

CRF has been found to be associated with behavior. Physical activity is inversely correlated with fatigue. In fact, reduced activity and lack of motivation are hallmarks of CRF and the resulting inactivity likely serves to perpetuate the fatigued condition (Ahlberg, Ekman, Gaston-Johansson, & Mock, 2003). The deconditioning (i.e., loss of physical fitness) that follows inactivity has generally been recognized as a "potent cause" of fatigue in chronic fatigue patients and other medical conditions (Wessely, Hotopf, & Sharpe, 1998), and such effects have been found in studies with breast cancer patients (Ahlberg et al., 2003). As a fatigued individual becomes increasingly deconditioned over time, energy and motivation to resume activity that could halt the deconditioning process diminishes, resulting in a vicious, perpetuating cycle that is difficult to correct. Fatigue has been found to have a profound and pervasive impact on cancer patients' ability to perform activities of daily living. Moreover, the decreased motivation to engage in usual activities may lead to impaired social and occupational functioning. (Hofman et al., 2007).

In terms of cognitive variables, catastrophizing and rumination appear to play a role in patient's adjustment to cancer (Schroevers, Kraaij, & Garnefski, 2008), and a body of research has found consistent support for a connection between catastrophizing and higher levels of fatigue (Andrykowski, Schmidt, Salsman, Beacham, & Jacobsen, 2005; Broeckel, Jacobsen, Horton, Balducci, & Lyman, 1998; Donovan, Small, Andrykowski, Munster, & Jacobsen, 2007; Jacobsen, Andrykowski, & Thors, 2004). Catastrophizing has been defined as dwelling on the most extreme negative consequences conceivable when confronted with a situation in which there is any possibility of an unpleasant outcome (Beck, 1979). This negative ruminative focus, which has been characterized by an analytical evaluative self-focus (i.e., thinking about the causes, meanings, and consequences of an event) is associated with negative affect (Rimes &

Watkins, 2005), which could play a role in the development and maintenance of CRF. In a study of 288 women undergoing adjuvant therapy for early-stage breast cancer, a tendency to catastrophize in response to fatigue or treatment was associated with incidents of CRF at post-treatment assessment. In fact, each 1-point increment of self-reported catastrophizing was associated with a 14% increase in risk for developing CRF over the course of adjuvant therapy (Andrykowski et al., 2005).

A related cognitive process that has been found to be significantly associated with CRF in at least one study is negative beliefs about activity. Young and White (2006) investigated a cognitive-behavioral model of fatigue in a sample of 69 disease-free breast cancer patients. The model was derived from work in CFS suggesting that the inactivity that maintains fatigue is associated with a belief that activity should be avoided to prevent worsening of the underlying cause of the fatigue. In Young and White's study, negative beliefs about activity emerged as a significant predictor of CRF in regression analysis. This finding, although preliminary and limited by the small sample size, suggests that beliefs about activity may be an important perpetuating factor of CRF.

Sleep disturbance is another prevalent and undertreated symptom in cancer patients that, not surprisingly, has been found to have a clear association with fatigue. Reviewers of the extant studies of the associations of the two symptoms have concluded that, although more research is needed, it is likely that sleep and CRF are reciprocally related. These reviewers stated that targeting either symptom in treatment may help with the other (Roscoe et al., 2007). A recent review of 34 studies reporting associations of CRF to insomnia found an average correlation of 0.34 (Donovan & Jacobsen, 2007). The authors concluded evidence supports assessing and treating fatigue, depression, and insomnia together as a symptom cluster in cancer patients.

Notably, cognitive and behavioral variables that have been found to be associated with fatigue—catastrophizing, negative ruminative focus, sleep disturbance, and reduced activity—are also frequently included in cognitive-behavioral models of depression (Beck, 1979; Hollon, Haman, & Brown, 2002).

Assessing CRF

Fatigue is by nature a subjective symptom and therefore it is most often measured by self report. To an individual suffering from it, CRF is a symptom that is "felt" rather than objectively manifested (Krishnasamy & Field, 2004), and participants in qualitative studies have reported that fatigue affected them physically, mentally, socially, and emotionally (Armes, 2004). Individuals who experience CRF have found it relatively easy to convey the physical or functional aspects but making the emotional and psychosocial aspects accessible to others has been more difficult (Krishnasamy & Field, 2004). Krishnasamy included the following statement of a case study participant to illustrate this difficulty:

> It's hard to tell you or tell really anyone what it's like because it's something that you feel all over, inside and outside…it's like pulling down inside when you have to fight even to stand up. Some days it's hard to imagine I will ever be able to do anything again and I can feel myself in danger of just giving up, that's what it's like, but I don't know if that makes sense to you or anyone but me (p. 130).

Some scientists have proposed that CRF is best assessed as a syndrome. Consequently, a standard set of diagnostic criteria has been added to the recently revised ICD-10 (*International Statistical Classification of Diseases and Related Health Problems--10th Revision*, 2007). 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 (Cella, Davis, Breitbart, & Curt, 2001). These criteria have not yet achieved expert consensus or validation, however, and most research studies simply measure fatigue, either in a simple or multidimensional fashion.

A review of the literature on CRF measurement (Wu & McSweeney, 2004) reported having found evidence that health professionals are increasingly receptive to assessing CRF and incorporating the patients' perspective in that assessment. Work has expanded in the development of multidimensional measures of CRF to go along with simple, single-item screening measures, and both existing and new measures are being psychometrically tested and revised. A continuing problem, however, is lack of

consensus on the definition of CRF and which measurement approach is best. A recent review (Jean-Pierre et al., 2007) 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 non-specific to cancer.

Biological Mechanisms of CRF

Although potential biological mechanisms have been proposed, relatively little basic research to date has focused on fatigue in general and even less on CRF (Gutstein, 2001). Andrews and colleagues (2004) noted that CRF's complexity and multidimensional nature makes it a difficult symptom to study. Moreover, fatigued patients can be especially difficult to recruit for research participation—and those who do participate may be suffering detrimental effects on concentration or attention that may interfere with research activities. The consequent dearth of empirical evidence regarding the physiological mechanisms of CRF has led to a reliance on descriptive and correlational studies to inform treatment. Extant conceptualizations of possible mechanisms are mostly derived from research carried out in non-cancer populations in the context of physical exercise or diseases other than cancer such as chronic fatigue syndrome (CFS) and rheumatoid arthritis (Ryan et al., 2007). CRF differs substantially from the fatigue associated with exercise, which is readily relieved by rest (Andrews et al., 2004). Fatigue experienced by cancer patients may have more in common with the experience of those diagnosed with CFS, although differences as well as similarities have been noted by the few investigators who have addressed this issue (Bennett, Goldstein, Friedlander, Hickie, & Lloyd, 2007; Servaes, van der Werf, Prins, Verhagen, & Bleijenberg, 2000; Wessely et al., 1998).

Biological mechanisms that have been proposed for CRF include dysregulation of cytokines, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, abnormal accumulation of muscle metabolites, changes in neuromuscular function, abnormalities in adenosine triphosphate synthesis, serotonin dysregulation, vagal afferent activation, and circadian rhythm dysfunction (Berger et al., 2008; Ryan et al., 2007). A recent review

(Miller, Ancoli-Israel, Bower, Capuron, & Irwin, 2008) reported that immunologic processes have been receiving special attention in the search for mechanisms to explain what they characterized as "behavioral alterations" but are in essence symptoms (i.e., depression, fatigue, sleep disturbance, and cognitive dysfunction) common in patients with cancer. The authors presented data indicating that increased inflammatory responses triggered by cancer and its treatments may interact with pathophysiologic pathways known to be involved in the regulation of common cancer-related symptoms. Specifically, activation of innate immune inflammatory response and its regulation through neuroendocrine pathways are hypothesized to influence CNS functions including neurotransmitter metabolism, neuropeptide function, sleep-wake cycles, and regional brain activity. The ultimate result may be mediation of the development of fatigue, depression, impaired sleep, and cognitive dysfunction. The review included discussion of studies finding an association between inflammatory markers and fatigue in cancer patients and compared these to other studies reporting negative findings. The authors concluded that alterations in cortisol secretion in response to the stress of cancer may play a role in inflammatory dysregulation which may be a mechanism underlying fatigue. They also cited a recent meta-analysis as further support for their model (Schubert, Hong, Natarajan, Mills, & Dimsdale, 2007). The meta-analysis authors pooled correlation coefficients from 18 studies and found that CRF was positively associated with inflammatory markers.

Depression in Cancer

Depression occurs in about 10% to 25% of people with cancer, a rate estimated to be at least four times greater than in the general population (Carr et al., 2002; Pirl, 2004) but similar to rates of depressive states in patients similarly ill with other medical diagnoses (Spiegel & Giese-Davis, 2003). Prevalence rates in cancer patients have been found to be similar whether depression is identified as a set of symptoms or as a clinical syndrome such as a major depressive disorder (MDD). A recent review (Pirl, 2004) concluded that a majority of studies diagnosing MDD as a syndrome using *Diagnostic*

and Statistical Manual of Mental Disorders (DSM) criteria found rates of between 10% and 25%; a majority of studies using a standardized instrument to measure prevalence of depressive symptoms fell into the range of 7% to 21%. Some of the variance across studies was attributed to heterogeneity in the population samples in terms of cancer type, hospital status, disease or treatment status, and differences among authors in choosing cutoff scores.

Risk of developing depression in cancer patients may vary by type of treatment (Raison & Miller, 2003). Certain cytokines and other cancer-related medications are frequently associated with depression. Some evidence suggests oncologic surgery may also increase the risk of developing depression.

An Overlooked Symptom

Similarly to fatigue, depression has been under-diagnosed and undertreated in cancer patients (Bottomley, 1998; Spiegel & Giese-Davis, 2003). Evidence suggests that depression may go unrecognized by internists treating medically ill outpatients in 50% to 75% of cases (McDaniel, Musselman, Porter, Reed, & Nemeroff, 1995). Depression may be overlooked partly because the symptoms are considered to be a normal and inevitable reaction to serious disease and partly because some of the signs of depression (e.g., weight loss and sleep disturbance) can also be attributed to the disease itself (Raison & Miller, 2003; Spiegel & Giese-Davis, 2003). Recognizing and treating depression is considered crucial in medically ill patients, however, not only to enhance quality of life but because it may adversely affect compliance with treatment, length of time in the hospital, and ability for self-care (McDaniel et al., 1995).

Assessing Depression

The broad range of states and symptoms encompassed within the construct of depression complicates its assessment. “Depression” may refer to a mood state, the diagnosis of a clinical syndrome such as MDD, or it may refer to one or a group of

symptoms such as sad mood, anhedonia, anorexia, weight loss, and sleep disturbance (Ingram & Siegle, 2002; Raison & Miller, 2003). Ingram and Siegle (2002) discussed the arbitrariness of depression as a theoretical construct—determined as it is by a collective decision by the scientific community to formally recognize certain symptoms (e.g., sad mood) and not others (e.g., being discouraged about the future). Because of the lack of standardization in diagnosing depression, some have advocated assessing depression in medical patients through biological markers such as neuroendocrine alterations, changes in serotonergic neurotransmission, alterations in sleep architecture, or structural brain abnormalities. However, no biological marker has yet been identified to be sensitive and specific enough for depression diagnosis, and few studies have taken up this assessment method (Massie & Popkin, 1998).

The clinical interview is considered standard for diagnosing MDD in cancer patients. As for assessing depressive symptoms, no clear standard has been established, according to the findings of a recent review, although the Hospital Depression and Anxiety Scale (HADS) was used most frequently to measure depressive symptoms (Pirl, 2004). Many instruments are in use, some of which were created for cancer patients, and they range in complexity from simple visual analog scales to multidimensional instruments including quality-of-life assessment. In research, depression is often operationally defined as scoring above a cutoff score on a self-report questionnaire (Ingram & Siegle, 2002).

Assessment of depression in cancer patients is confounded by physical symptoms that are associated with both depression and the disease or its treatment (Pirl, 2004). Raison and Miller (2003) discussed the overlap of depressive symptoms with those often observed in the context of illness such as cancer. To illustrate the scope of the problem, these authors listed 13 signs and symptoms, 9 of which were common to both major depression and cytokine-induced sickness behavior (often present in cancer patients). The symptoms common to both were anhedonia, social isolation, fatigue, anorexia, weight loss, sleep disturbance, cognitive disturbance, decreased libido, and psychomotor retardation. Hyperalgesia (i.e., increased sensitivity to pain) distinguished sickness

syndrome from depression, and symptoms that help to distinguish major depression were depressed mood, guilt/worthlessness, and suicidal ideation.

The problem of overlap of symptoms across clinical syndromes extends to the current study in important ways. The fact that fatigue is a symptom of sickness behavior and also depression poses special challenges in efforts to understand the interrelationship of CRF and depression.

Associations of CRF and Depression

Fatigue and depression are symptoms of similar importance in cancer care, as both conditions occur more frequently in cancer patients than in the general population and both can be highly distressing and disabling. With the recent emphasis on assessing and treating CRF, researchers and clinicians need to better understand how fatigue and depression interrelate in the cancer context. It is well established that fatigue is both a symptom of certain depressive disorders *and* a symptom of cancer and its treatment. It is also generally known that depression is, like fatigue, often present in patients with cancer. Beyond that, many aspects of the relationship require clarification through future investigation. For example, to what degree do fatigue and depression conceptually differ, to what degree do they co-occur, and are there causal relationships (Jacobsen, Donovan, & Weitzner, 2003)? In terms of treatment, does intervening on depression lead to relief from fatigue as well? The answers to these questions will ultimately aide both researchers and clinicians who are seeking better ways to assess and treat fatigue in cancer care settings.

Extant literature reveals significant correlations between fatigue and depression in cancer patients—sometimes at a relatively strong magnitude. For example, Jacobsen and colleagues (2003) conducted a review of CRF's association with depression. In 30 studies that assessed both fatigue and depression in patients with cancer, correlations between the two were all positive and ranged from 0.16 to 0.80. The average correlation across studies was 0.54. Another review focused on fatigue, depression, and insomnia as a potential symptom cluster, assessing the data from 16 studies that measured all three

symptoms (Donovan & Jacobsen, 2007). The correlations found for fatigue and depression were strikingly similar to that found by Jacobsen and Weitzner, with the average being 0.55, and a range of 0.16 to 0.80.

Elucidation of the other questions about the nature of the relationship between CRF and depression, however, is more limited in the literature. In fact, Jacobsen and colleagues (2003) found contradictory evidence regarding causal relationships in their review of 30 studies. They concluded some of the evidence suggested CRF could cause depression, some suggested that depression can cause CRF, and some indicated that both CRF and depression are caused by a common third factor.

Because the conceptual overlap and extent of co-occurrence of fatigue, depression, and anxiety is so pronounced, some authors have even examined the possibility that general fatigue (not necessarily in cancer patients) and psychiatric disorder (i.e., depression and anxiety) are actually one and the same (Reuter & Härter, 2004; Van Der Linden et al., 1999; Wessely et al., 1998). Wessely and colleagues (1998), who were primarily focusing on chronic fatigue syndrome, advanced an opposing argument that fatigue sometimes exists independently of psychiatric disorder.

Reuter and Härter (2004) mapped the multidimensional factors of fatigue as conceptualized in oncology settings against recognized factors of depression, placing them in categories of physical (i.e., loss of energy, decreased activity, decreased energy/tiredness, physical sensations, somatic/vegetative symptoms, sleep disturbance, and weakness); cognitive (i.e., decreased concentration and attention and loss of interest); and emotional (i.e., sadness, anxiety/tension, depressed mood/anhedonia, and psychomotor retardation or agitation), as presented in Table 1. They concluded that fatigue did not comprise any symptoms beyond those found in the context of depression, and that depression is the broader—possibly even subsuming—concept. Depression, they argue, extends beyond fatigue because of its unique cognitive and emotional aspects such as self-devaluation, feelings of emptiness and deadness, fear of the future, social withdrawal, and suicidal ideation. Taking into account the evidence found in studies relating to CFS suggesting fatigue as an entity independent of depression, these authors

advocated further exploration of the degree of independence between the two diagnostic entities for the potential to inform treatment for cancer patients.

Measurement Challenges

Measurement is an important issue in the study of the relationship between CRF and depression, particularly the ability to distinguish fatigue from depression. Both 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

Table 1

Symptoms of Fatigue and Depressive Disorders

Fatigue	**Depressive Disorders**
Physical	
Decreased activity	Loss of energy
Decreased energy/tiredness	Loss of energy
Weakness	Loss of energy
Physical sensations	Somatic-vegetative symptoms
Sleep disturbance	Sleep disturbance
Cognitive	
Decreased concentration and attention	Decreased concentration and attention
Loss of interest	Loss of interest
Emotional	
Sadness	Depressed mood, anhedonia
Anxiety/tension	Psychomotor retardation or agitation

(Reuter & Härter, 2004)

every day" is one of the core symptoms used in establishing a clinical diagnosis of depression (*Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revision*, 2000, p. 356). Both depression and fatigue can be assessed as a single symptom, a cluster of symptoms, or as a clinical syndrome (Arnold, 2008). Both are measured primarily by self report. Diagnostic criteria for depressive syndrome share several symptoms in common with the syndromal diagnostic criteria for CRF including fatigue, sleep disturbance, concentration difficulties, and decreased interest in usual activities.

The generally high positive correlations found on continuous measures of fatigue and depression administered together have led some to question the discriminant validity of the instruments in use (Jacobsen, 2004). However, some studies have found that the correlation of fatigue and depression remains high even after removing the fatigue items from depression measures (Smets, Garssen, Cull, & de Haes, 1996; Stone, Hardy, Huddart, A., & Richards, 2000; Stone, Richards, A'Hern, & Hardy, 2001). Furthermore, fatigue measures correlate rather strongly with measures that assess just the mood aspects of depression (Jacobsen & Weitzner, 2004). Some have suggested that the overlap problem may be avoided in fatigue assessment 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?" (Jean-Pierre et al., 2007). Others have proposed that CRF is best measured as a syndrome, using the set of diagnostic criteria that has been proposed for future inclusion in the *International Classification of Diseases Tenth Edition* (Cella et al., 2001).

Because measurement may confound attempts to understand the relationship between CRF and psychological variables, it was included as a secondary topic in a systematic review of studies undertaken during development of the current study (Brown & Kroenke, 2009). Anxiety correlations are also included in the review because no previously published systematic review has reported anxiety's association with CRF even though many investigators have included analysis of anxiety as an adjunct to investigating depression's associations with fatigue in cancer.

Systematic Review of Associations of CRF with Depression and Anxiety

In a systematic review of the literature (Brown & Kroenke, 2009), studies were included that reported the associations of CRF with depression or anxiety or both. Associations were reported either as correlation coefficients or odds ratios. Tabulated summary information for each study can be found in Appendix B.

The total number of participants from 61 studies was 12,704. Depression was significantly related to CRF in all the studies that reported the association except one, and in some cases the magnitude was strong. The range of correlation coefficients between fatigue and depression in 52 studies reporting this statistic was 0.16 to 0.84. The average correlation, weighted by sample size, was 0.56 (95% CI, 0.54 to 0.58). For the three studies reporting odds ratios, the weighted average association of fatigue with depression was 1.16.

Anxiety was significantly correlated to fatigue in 33 of the 35 studies reporting the association. The range of correlation coefficients was 0.16 to 0.73, and the weighted average was 0.46 (95% CI, 0.44 to 0.49). The weighted mean for the two studies reporting odds ratios was 1.19.

Thirty-one different instruments were used to assess fatigue in the 61 studies in the review, demonstrating the lack of consensus about the best way to measure fatigue in cancer research. No single scale predominated. The instrument used most frequently, the Multidimensional Fatigue Inventory, was used in only 9 studies. In contrast, depression was measured with 12 instruments across all the studies. Two scales predominated for measuring depression—a subscale of the HADS (Zigmond & Snaith, 1983) was used in 24 studies, and the Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977) was used in 15.

A few investigators addressed the issue of measurement overlap between fatigue and depression by dropping certain items from depression instruments that were identified as most likely to reduce discrimination of separate constructs. Dropped items typically assessed physical or somatic symptoms or were otherwise deemed as similar to fatigue (e.g., “I feel as if I am slowed down”). Significant relationships were found in all the studies that dropped items except one.

Twenty-five of the studies were longitudinal. Of these, 17 investigated associations between fatigue and depression or anxiety at multiple time-points. These studies were examined for patterns to explicate the interrelationships between fatigue and depression. No clear pattern was identified, partly due to heterogeneity of the samples between studies and partly due to inconclusive or contradictory findings. In only 2 studies did the authors clearly assert that their findings suggest that changes in fatigue were associated with changes in depression and anxiety (Stone et al., 2001; Tchekmedyian, Kallich, McDermott, Fayers, & Erder, 2003). Authors of at least 6 studies concluded that no evidence of relationships with longitudinal changes in fatigue had been found—4 of which referred to depression but not anxiety (Morrow et al., 2003; Pirl, 2008; Schumacher et al., 2002; Visser & Smets, 1998), and 2 assessing both depression and anxiety (Geinitz et al., 2001; Stone, Hardy et al., 2000). Authors of the remaining studies reported findings that were relatively ambiguous on this matter.

The 8 studies that did report conclusions about longitudinal relationships between fatigue and depression are particularly germane to the current study and therefore warrant further elucidation. Stone and colleagues (2001) studied fatigue, depression, and anxiety in patients with breast cancer (n = 34) or prostate cancer (n = 35) before RT and within a week after treatment completion. Of 5 fatigue measures, 3 showed a significant increase in fatigue over the course of RT. Small but significant increases in depression scores were associated with small increases in fatigue scores. A combination of fatigue and anxiety scores at baseline was able to predict 54% of the variation in fatigue scores at the completion of RT. It is important to note, however, that the scale that was designated *a priori* as the primary fatigue measure (the Fatigue Severity Scale) failed to demonstrate a significant increase. Moreover, while the increases shown by 3 other measures of fatigue were significant, the magnitude of change was relatively modest. These two issues cast doubt on the findings.

The other study that found associations between changes in fatigue and changes in depression was with a sample of patients receiving chemotherapy for lung cancer (n = 250) and participating in a randomized, double-blind, placebo-controlled trial of darbepoetin alfa for treatment of anemia. The participants were assessed for fatigue,

depression, and anxiety at baseline and between the 4th and 12th week of treatment (Tchekmedyian et al., 2003). Improvements in fatigue were associated with reductions in anxiety and depression.

One of the studies finding no associations between changes in fatigue and changes in depression was that of Morrow and colleagues (2003). In this randomized, double-blind placebo-controlled trial involving 549 cancer patients undergoing chemotherapy, depression was affected by the intervention (paroxetine compared to placebo) while fatigue was not. In a study of 52 men with prostate cancer receiving hormone therapy (Pirl, 2008), fatigue increased significantly over the 12-month study period but depression did not change. In another study, Schumacher and colleagues (2002) evaluated QoL in 101 patients undergoing treatment for acute myeloid leukemia. Assessment was done at 12 time-points. Depression was significantly inversely correlated with the emotional functioning subscale of the European Organization for Research and Treatment of Cancer QLQ-C30 throughout the study but its correlation with the fatigue subscale was nonsignificant at 5 of 12 time-points.

Another study that found no evidence for a cause-and-effect relationship between fatigue and depression was that reported by Visser and Smets (1998). These researchers examined a heterogeneous sample of 250 cancer patients before treatment, two weeks after treatment, and nine months after treatment. Fatigue remained stable or increased just after radiotherapy, depending on the dimension being considered, whereas depression decreased. Nine months later, fatigue had decreased while depression remained stable. In another study of 41 breast cancer patients (Geinitz, 2001), fatigue increased during RT and returned to pretreatment levels 2 months after treatment. Although anxiety and depression were found to be associated with fatigue, neither the anxiety nor the depression scores increased significantly during RT, arguing against these variables explaining radiation-related fatigue.

The sixth study that found no relationship between changes in fatigue and changes in depression was reported by Stone and colleagues (2000). They examined fatigue in 62 outpatients with prostate cancer before hormone therapy treatment and 3-months after treatment. They noted that increases in fatigue were not related to any increase in

psychological complaints, including depression, even though a strong relationship existed at baseline.

Our own review (Brown & Kroenke, 2009) concluded that depression and anxiety are both important correlates of CRF, with depression having the stronger association of the two. The findings supported the conclusions of previous reviews of psychological correlates of CRF (Donovan & Jacobsen, 2007; Jacobsen et al., 2003; Jacobsen & Weitzner, 2004; Servaes, Verhagen et al., 2002). The heterogeneity of the 61 studies, however, precluded specific conclusions about the directionality or mechanisms underlying the relationships among fatigue and depression. Moreover, the inconsistent findings in the subset of longitudinal studies support suggestions in the literature that development of CRF may involve several physiological, biochemical, and psychological systems (Ryan et al., 2007) that may vary by cancer site, stage of disease, and type of treatment.

Intervention studies aimed at improving outcome variables that are correlated with CRF may also be helpful in teasing apart the interrelationships (Hotopf, 2004). 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. The study by Tchekmedyian and colleagues (2003) is one such example, and it has provided the single most compelling finding suggesting that changes in fatigue are associated with changes in depression. These findings are contradicted, however, by the randomized, double-blind placebo controlled trial of Morrow and colleagues (2003), in which depression was affected by the intervention (paroxetine compared to placebo) while fatigue was not. This trial specified elevated fatigue as an inclusion criterion—important in this type of research.

The measurement challenges associated with studying CRF's relationship to depression demand careful attention in future studies. Research in this domain will benefit if the field of fatigue instruments is narrowed to a few that have been well-validated to accurately assess CRF and distinguish it from depression.

Statement of the Problem

The current research was undertaken to add to the understanding of the nature of the relationship between fatigue and depression in cancer patients. Although evidence in the literature demonstrates a clear association between the two symptoms, studies examining directional or causal relationships are too few and the findings too inconsistent to draw conclusions. Many investigators working in this domain have called for more longitudinal research in cancer patients who report symptoms of fatigue and depression. They emphasize a need for careful measurement and analysis of how the relationships either change or stay the same over time. The current study analyzed the pathways among these symptoms in search of evidence suggesting possible causal relationships.

A Cognitive Behavioral Model of Fatigue

Primarily in the context of chronic fatigue syndrome, Wessely, Hotopf, and Sharpe (1998) proposed a cognitive behavioral model that recognizes the multidimensionality of persistent fatigue and distinguishes between factors that are predisposing, precipitating, or perpetuating. The authors supported this model by discussing "mutually reinforcing vicious circles" of interacting beliefs, emotions, physiology, and behavior hypothesized as perpetuating an extant illness such as fatigue:

> The experience of symptoms, and fears about their meaning, interfere with the normal physiological and psychological processes required for effortful activity or cognitive processes. The consequence of increased concern is heightened awareness, selective attention, and 'body watching', which can then intensify both the experience and perceived frequency of symptoms, thereby confirming illness beliefs and reinforcing illness behaviour. This in turn contributes to a vicious circle of increasing symptomatic distress and increasing restriction of activity in order to cope with such symptoms. The more activity is avoided, the worse are the symptoms whenever it is attempted, thus providing further validation of the accuracy of the person's illness beliefs. Episodic attempts to be active merely

serve to strengthen the patient's belief conviction of suffering from an insurmountable disease and leads to further concern about symptoms (p. 277). The core of the hypothesized model is the notion that what triggers an episode of fatigue may not be what keeps it going.

Hotopf (2004) presented a version of this model relating it to general fatigue and discussed its potential for consideration in a cancer context. In his presentation, predisposing factors of acute fatigue included past psychiatric disorder, somatic attributional style, early illness experience, and genetic factors. The precipitating event might be a serious viral infection, life event, or surgery. Perpetuating factors in the model that might result in chronic fatigue included behavioral, cognitive, emotional, physical, and social constructs. The model itself is untested (M. Hotopf, personal email communication, May 30, 2008) although extant literature provides support for the constructs that are included. The model for the current study at Figure 1 represents a further adaptation of the one published by Hotopf. This modified version incorporates findings in the literature specific to CRF. For this study, it will be referred to as the perpetuating factors model, as that category of factors supports the main hypotheses.

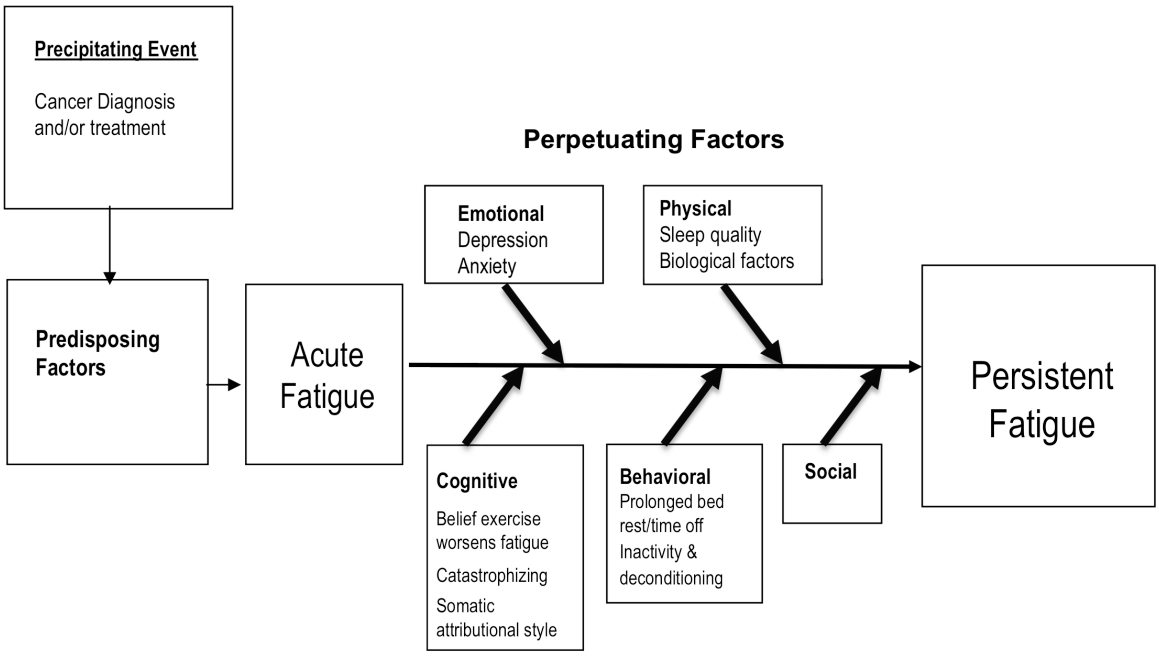

Figure 1. Perpetuating factors of cancer-related fatigue

Existing literature was surveyed for evidence about the degree to which the perpetuating factors model as proposed for CFS (Wessely et al., 1998) might also be applicable in a cancer context. At least two studies have been published comparing the experience of CRF with that of CFS. An investigation comparing 57 patients with fatigue after breast cancer treatment to 57 gender- and age-matched patients with CFS (Servaes, Prins, Verhagen, & Bleijenberg, 2002) found both similarities and differences between groups. CFS patients' scores were more problematic in level of fatigue, functional impairment, physical activity, pain, and self-efficacy; however, problems were similar between the two groups in terms of psychological well-being, sleep, and concentration. The authors concluded that interventions targeting the cognitive and behavioral perpetuating factors of fatigue would be relevant for CRF as well as for CFS but modifications would be needed, possibly emphasizing depression, sleep, and concentration problems. A qualitative study (Bennett et al., 2007) compared the experience of 16 women with post-cancer fatigue and 12 women with CFS. The analysis revealed that both groups reported "remarkably similar" symptoms featuring fatigue, cognitive difficulties, mood disturbance, and disabling behavioral consequences. Both groups had similar levels of sleep disturbance. Women with CFS reported additional symptoms of musculoskeletal pain and influenza-like manifestations. Mood disturbance was prominent in the descriptions provided by the women with CRF. The authors concluded that CRF appeared to be qualitatively similar to CFS.

Another study (Vercoulin et al., 1998) presented findings relating to perpetuating factors of chronic fatigue, although it did not test fatigue in cancer patients. Vorcoulin and colleagues tested a model of hypothesized cognitive and behavioral perpetuating factors of fatigue using path analysis comparing CFS patients (n = 51) with patients with multiple sclerosis (MS; n = 50). Hypothesized perpetuating factors for fatigue included depression, causal attributions, sense of control, and physical activity. Results of a structural equation modeling analysis led the researchers to drop depression from the causal model and to add focusing on symptoms as a perpetuating factor, resulting in a good fit for the model in CFS patients but not in MS patients. The authors concluded that the findings of this study, along with other evidence in the literature, suggest that current

depression does not predict improvement in fatigue and that mood disorder is not an essential factor in perpetuating fatigue. Methodological problems with this study must be taken into account, however. The study was cross-sectional although longitudinal data is preferable in causal path analysis. Moreover, the sample size of 101 may have been too small to support the conclusions. Structural equation modeling is generally understood to be a large-sample technique, with 200 being the commonly accepted minimum for "large" samples (Kline, 2005).

To summarize, evidence is sufficient to support the co-occurrence of fatigue and depression in cancer patients. Evidence also appears to support the existence of depression and fatigue as two independent entities in cancer patients, albeit with substantial overlap. The literature is inconclusive, however, about whether depression exerts causal effects on fatigue, fatigue exerts causal effects on depression, the symptoms are the result of one or more common causes, or whether some combination or interaction among these possibilities exists. Of 17 longitudinal studies examining the relationship, 2 found fatigue and depression changed together in CRF, 6 found no evidence that changes in fatigue were associated with changes in depression, and the remaining studies were ambiguous on this matter. A model of fatigue proposed in the literature has hypothesized depression as a perpetuating factor in chronic fatigue, and a small body of evidence supports extending that model to a cancer context. A single study with methodological flaws concluded that depression is not important to perpetuation of fatigue in CFS patients. More longitudinal research, therefore, is warranted to determine how depression and fatigue are related in cancer patients.

Purpose

The current study examined the relationship of depression and fatigue over time in a heterogeneous sample of cancer patients. The perpetuating factors model of CRF provided theoretical support for the study hypotheses (Figure 1). Depression was expected to be supported as a perpetuating factor of fatigue by demonstrating that depression is causally related to fatigue. If depression is supported as a perpetuating

factor of CRF, then interventions targeting depressive symptoms may be appropriate in treating cancer patients who report they are suffering from fatigue.

Study Aims

The aim of this study was to examine whether depression exerts causal influence on fatigue over time in cancer patients. The existence of reverse or reciprocal effects (i.e., causal influence of fatigue on depression or bi-directional pathways) was also examined.

Hypothesis 1

In a heterogeneous sample of cancer patients, depression will predict changes in fatigue over 3 months. The association will be positive.

Hypothesis 2

Fatigue will also predict changes in depression over 3 months (reciprocal effects). This association will be positive but will be of lower magnitude than that between depression and changes in fatigue.

METHODS

This study used a single-group cohort design in a secondary analysis of longitudinal data from a randomized controlled trial (N = 405) of an intervention for pain and depression in cancer patients. Kurt Kroenke, MD, is the principal investigator. The Indiana Cancer Pain and Depression trial (INCPAD) is an NCI-funded study that tested the effectiveness of telecare management delivered by a nurse-psychiatrist team in a statewide network of urban and rural community-based cancer clinics. The intervention was based upon the empirically-validated Three-Component Model (TCM; Dietrich et al., 2004; Oxman, Dietrich, Williams Jr., & Kroenke, 2002). In INCPAD, the model was a collaboration between the oncology practice, a centralized nurse care manager, and a supervising pain-psychiatrist. A telemedicine approach was utilized with automated home-based symptom monitoring of pain and depressive symptomatology coupled with telephonic nurse care management over 12 months. Medication management utilized evidence-based algorithms for antidepressants and analgesics. Participants were assessed at baseline, 1, 3, 6, and 12 months by telephone interviewers blinded to treatment group. The sample included patients with cancer-related pain (n = 96), clinical depression (n = 131), or both (n = 178). Participants were randomized by computer to either the intervention or usual care control group, stratified by symptom type. Participants were enrolled from March 2006 to August 2008. Details of the study design and longitudinal outcomes have been published (Kroenke et al., 2009; Kroenke et al., under review). To summarize, patients in the intervention group had greater improvements than the usual care control group in both depression and pain at all time points including 12 months.

Participants

Participants were recruited for the INCPAD study from 16 oncology clinics affiliated with the Community Cancer Care (CCC) network in Indiana. Cancer types included breast (29%), lung (20%), gastrointestinal (17%), lymphoma or hematological (13%), genitourinary (10%); and other (10%). Forty-two percent were in a maintenance phase or disease-free status, 37% were newly diagnosed, and 20% were experiencing recurrent or progressive cancer. Ages ranged from 23 to 85, with the average being 58 (SD = 10.8). The sample was 68% female. About half (49%) were married. The majority were Caucasian (80%). Education was mixed: 12% were college graduates, 27% had attended some college or trade school, 40% had a high school diploma or GED, and 22% had not finished high school. Overall, the sample had a relatively low income (only 25% reported a "comfortable level of income"); 20% were employed, whereas 43% were unable to work due to health or disability, and 29% were retired. Baseline characteristics are further detailed in Table 2.

Although the INCPAD sample was recruited based on clinically significant pain or depression, baseline data indicates a high prevalence of fatigue . In fact, in a published secondary analysis of somatic symptom burden in INCPAD, fatigue was reported to be the most bothersome symptom among the 22 symptoms assessed, with 98% of the sample reporting feeling tired and 79% reporting being "bothered a lot" by this symptom (Kroenke et al., In Press). Moreover, the mean score on the SF vitality scale was 28.26 (SD = 19.2), which exceeded the established cutoff for clinically significant fatigue.

Procedures

To identify eligible participants for the INCPAD study, oncology clinic staff members asked patients to complete a 4-item depression and pain questionnaire, which is a combination of 2-item screeners that are both well-validated for assessing depression and pain severity. The PHQ-2 depression scale (Kroenke, Spitzer, & Williams, 2003) is drawn from the 9-item Patient Health Questionnaire (PHQ-9) and the pain screener is the SF-36 bodily pain scale (Ware, Kosinski, & Keller, 1994).

Table 2

Baseline Characteristics • Bold value in range indicates worse score	**Full INCPAD sample N = 405**	**Panel Analysis sample n = 329**	***P* Value**
Mean (SD) age, yr	58.8 (10.8) range 23 - 85	58.5 (10.5) range 29 - 85	.70
Female sex, n (%)	275 (68)	228 (69)	.61
Race, n (%)			
White	322 (80)	260 (79)	.95
Black	73 (18)	61 (18)	.93
Other	10 (2)	8 (2)	.84
Education, n (%)			
Less than High school	87(21)	68 (21)	.86
High school	160 (40)	131 (43)	.40
Some college or trade school	108 (27)	89 (27)	.97
College graduate	50 (12)	41 (12)	.95
Married, n (%)	199 (49)	159 (48)	.84
Employment status, n (%)			
Employed	81 (20)	65 (20)	.99
Unable to work--poor health/disability	176 (43)	148 (45)	.74
Retired	117 (29)	92 (28)	.85
Other	30 (7)	24 (7)	.94
Comfortable level of income, n (%)	100 (25)	81 (25)	.95
Mean (SD) no. of medical diseases	2.08 (1.6)	2.09 (1.6)	.93
Mean (SD) scores *			
SF Vitality Scale Total (score range, **0**-100)	28.26 (19.2)	29.12 (19.6)	.58
BPI pain severity (score range, 0-**10**)	4.27 (2.4)	4.20 (2.3)	.69
SCL-20 depression (score range, 0-**4**)	1.44 (0.7)	1.43 (0.7)	.85
Sheehan Disability Index (range, 0-**10**)	5.44 (2.9)	5.34 (2.9)	.67
Overall quality of life (score range, **0**-10)	5.62 (2.3)	5.67 (2.3)	.82
Mean disability days in past 4 weeks			
Bed days	5.6 (7.7)	5.78 (7.7)	.75
Days in which activities reduced by ≥ 50%	11.2 (9)	10.97 (9)	.75
Currently w/ mental health provider, n (%)	44 (11)	38 (12)	.76

Baseline Characteristic	Full INCPAD sample N = 405	Panel Analysis Sample N = 329	*P* Value
Type of cancer, n (%)			
Breast	118 (29)	106 (32)	.42
Lung	81 (20)	60 (18)	.56
Gastrointestinal	70 (17)	57 (17)	.77
Lymphoma and hematological	53 (13)	41 (13)	.77
Genitourinary	41 (10)	33 (10)	.90
Other	42 (10)	32 (10)	.94
Phase of cancer, n (%)			
Newly-diagnosed	150 (37)	126 (38)	.84
Maintenance or disease-free	172 (42)	146 (44)	.64
Recurrent or progressive	83 (20)	57 (17)	.35

Patients who screened positive for pain or for depression and expressed potential study interest in writing were contacted by telephone for an eligibility interview. The study was described in detail to those found to be eligible. Informed consent was audiotaped, with written consent obtained by follow-up mail. A baseline interview was completed after which the subject was randomized to either the intervention or usual care group.

All assessments were administered by telephone interview. Table 3 presents an assessment timetable for the key constructs relevant to the current study, along with the instrument used, number of items, and, in appropriate cases, Cronbach's coefficient alpha. Interviews were administered at baseline and at the end of month 1, 3, 6, and 12 and include additional questionnaires not listed in the table because they are not relevant to the aims of the current study. To minimize patient burden, some measures, including those for fatigue, were not included in the 1- and 6-month interviews.

Participants in both arms received $25 gift cards for each of 5 telephone research interviews. The oncology practice received $85 per enrolled patient for screening patients and providing medical record information for those enrolled. The current study analyzed data at baseline and 3 months.

Table 3

Study instruments

Domain	Measure	Items	Alpha*	Schedule				
				0 mo	1 mo	3 mo	6 mo	12 mo
Demographics	age, race, sex, education, marital, job status, income		n/a	X				
Medical comorbidity	Checklist of 8 conditions	8	n/a	X				
Depression	• Patient Health Questionnaire (PHQ)	9	0.81	X		X		X
	• SCL-20 depression scale	20	0.88	X	X	X	X	X
	• SF-36 Mental Health Inventory Depression	3	0.77	X		X		X
Fatigue	• SF-36Vitality scale	4	0.76	X		X		X

* Cronbach's coefficient alpha at baseline for internal reliability of the scale; N = 405.

INCPAD Eligibility

To be eligible for the INCPAD study, cancer patients met study criteria for either pain or depression. Depression was required to be of at least moderate severity, operationalized as a PHQ-9 score of 10 or greater with endorsement of depressed mood and/or anhedonia. In past research, over 90% of patients meeting these criteria had major depression and/or dysthymia, and the depression of the remaining patients was clinically significant with substantial functional impairment (Kroenke, Spitzer, & Williams, 2001a; Kroenke, West et al., 2001). Patients were eligible to be enrolled for pain if they had a score of 5 or greater on the Brief Pain Inventory (Cleeland, 1991) suggesting moderate severity, provided that the pain had persisted after use of at least 2 different analgesics and was cancer-related (i.e., not a pre-existing pain condition unrelated to cancer). Individuals were excluded if they did not speak English, had moderately severe cognitive impairment as defined by a validated 6-item cognitive screener (Callahan, Unverzagt,

Hui, Perkins, & Hendrie, 2002), had schizophrenia or other psychosis, had a pending pain-related disability claim, were pregnant, or were in hospice care.

During the 130-week enrollment period, 4,465 patients were screened in the 16 participating clinics. Of those, 1,851 screened positive for pain and/or depression and 616 were found to be eligible for the INCPAD trial (see flowchart, Figure 2). Of the 405 participants enrolled, 131 (32.3%) had depression only, 96 (23.7%) pain only, and 178 (43.9%) both depression and pain.

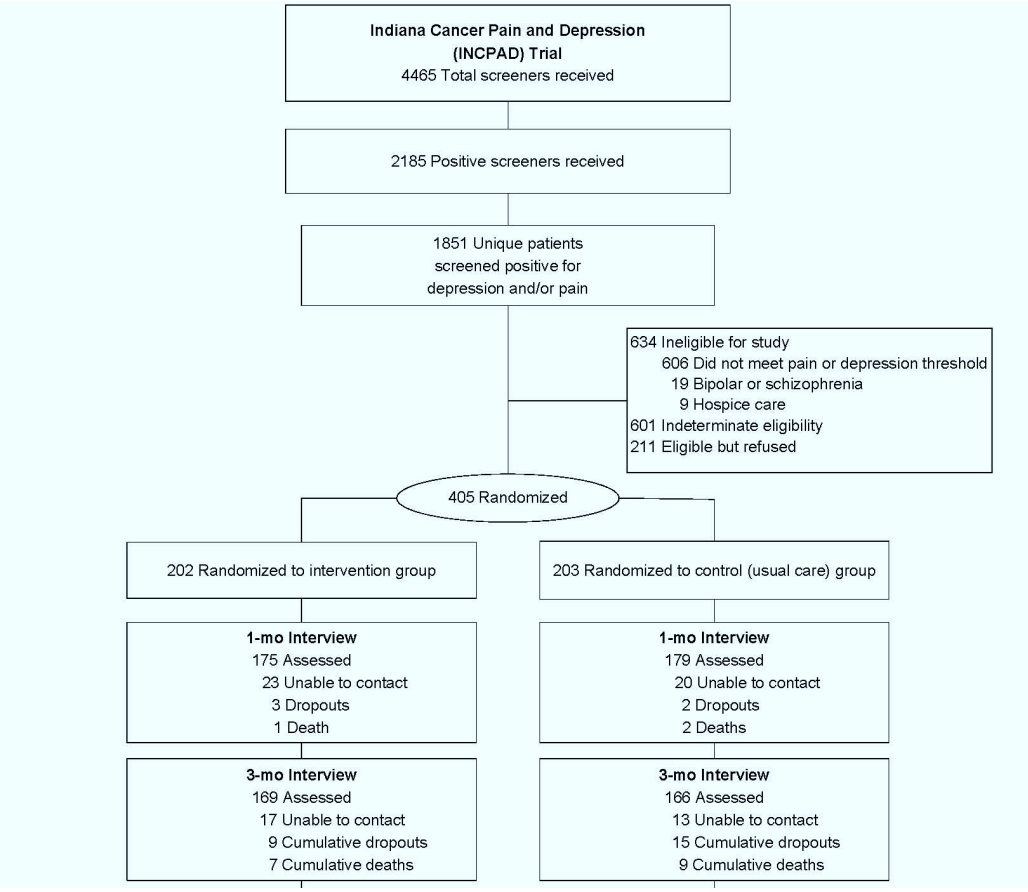

Figure 2. INCPAD trial flowchart

Measures

Vitality Scale of the SF-36. Fatigue was measured in the INCPAD study with the vitality scale of the SF-36 Health Survey, an instrument that assesses health-related quality of life (Ware, Snow, Kosinski, & Gandek, 1993). The 4 items of the vitality scale were each used as single-item indicators of the latent variable fatigue in the current study. The vitality scale was initially incorporated into the SF-36 to assess energy level and fatigue as a way to capture differences in subjective well-being. It asks respondents "How much of the time during the past 4 weeks "did you have a lot of energy?" "…have you felt full of life?" "…did you feel worn out?" and "…did you feel tired?" Respondents choose from a 5-level scale ranging from none of the time to all of the time. Standardized subscale scores range from 0 to 100, with higher scores indicating greater vitality. Norms for the vitality scale are based on a random general population sample of 2,457 (Ware et al., 1993). When analyzing the vitality scale as a dichotomous measure, previous researchers have categorized scores above the midpoint of 50 as representing well-being and scores below 50 as indicating disability due to fatigue (Bower et al., 2006). Moreover, the 25th percentile has been established in the literature as a clinically significant indicator of impairment; that is, those scoring below the 25th percentile (which was 45 for females in the U.S.).

The SF-36 has well established internal consistency, reliability, content validity, construct validity, and criterion-related validity, having been tested in a variety of population samples (Wu & McSweeney, 2004). The median reliability across multiple published studies was reported to be at or above 0.80 (Ware, Gandek, & IQOLA Project Group, 1994). Cronbach's coefficient alpha for the SF-36 is high across studies; in a validation study, it was greater than 0.85 (Brazier et al., 1992). In baseline data from the INCPAD study, Cronbach's coefficient alpha for the vitality scale was 0.77. The SF vitality scale has been widely used to assess fatigue across a range of conditions. A recent review (O'Connor, 2004) surveyed the number of citations in medical and psychology databases for commonly used measures of energy and fatigue and found the SF-36 vitality scale to be the most-cited, with 2,449 references. O'Connor found evidence to support the vitality scale's validity as a measure of the frequency of monthly feelings of

energy and fatigue, although he noted that with only 4 items, the scale may be limited in adequately representing all the facets of fatigue.

Convergent Validity

Multidimensional measures of CRF are becoming more common, as was seen in the review of 61 studies presented in the background section, whereas the vitality scale has been considered either a unidimensional scale of general fatigue (Jean-Pierre et al., 2007) or a bi-dimensional measure of energy and fatigue (O'Connor, 2004). To support the use of the vitality scale as a measure of fatigue in the cancer context, it was compared to a multidimensional instrument, the Fatigue Symptoms Inventory (FSI), which was developed specifically to assess fatigue in cancer patients. The FSI is a 13-item self-report instrument designed to measure the intensity and duration of fatigue and its interference with quality of life in cancer patients (Hann, Denniston, & Baker, 2000). Participants use 11-point scales to rate the *severity* of their fatigue in the past week in terms of worst, least, and average fatigue as well as fatigue "right now." *Frequency* is measured by number of days with fatigue in the past week (0-7 scale). Perceived *interference* is measured with 7 items on an 11-point scale assessing the degree to which fatigue in the past week is judged to interfere with general level of activity, ability to bathe and dress, normal work activity, ability to concentrate, relations with others, enjoyment of life, and mood. Convergent, divergent, and construct validity of the FSI has previously been established in samples of women undergoing treatment for breast cancer, women who had completed treatment for breast cancer, and women with no cancer history. Cronbach's coefficient alpha reliability for all subscales was found to be above 0.70. A mean score of ≥ 3 across the 3-item FSI severity composite has been established as the optimal cutoff for identifying clinically significant CRF (Donovan, Jacobsen, Small, Munster, & Andrykowski, 2008).

In INCPAD, the FSI was administered to a subset of participants during 1-month (n = 68) and 6-month (n = 96) interviews. These participants represented a consecutive sample of individuals undergoing 1- and 6-month interviews during this secondary

validation study in INCPAD. Results of the three subscales of the FSI were compared to the SF vitality scores and a single item from the PHQ-15 Somatic Symptom Scale (Kroenke, Spitzer, & Williams, 2001b). The PHQ fatigue item asks respondents to rate how bothered they have been by "feeling tired or having low energy" over the past 4 weeks. Response choices are "not bothered at all," "bothered a little," and "bothered a lot." Correlations among the scales were examined and the scales' effect sizes of change over 5 months were compared to evaluate sensitivity to patient-reported change.

Internal consistency was excellent for the vitality scale ($\alpha = 0.91$), and the FSI severity ($\alpha = 0.89$) and interference ($\alpha = 0.91$) subscales. Mean scores for both the FSI and the vitality scale demonstrated clinically significant fatigue in the subset sample, according to the established cutoffs of ≤ 45 for the vitality scale and ≥ 3 for the FSI severity composite (Table 4; Donovan et al., 2008). As expected, the vitality scale—with directionality that is the reverse of the FSI—was strongly inversely correlated with all three FSI scales. Moreover, both the FSI scores and the vitality score correlated strongly with the PHQ fatigue item in the expected directions, with the vitality scale having the strongest correlation (see Table 5).

To compare the scales' sensitivity to change, standardized response means (SRMs) were calculated for each fatigue scale, a method that has been used in previous studies

Table 4

Change Scores and Standardized Response Means (N = 58)

Fatigue measure	**Range ***	**1-month Mean (SD)**	**6- month Mean (SD)**	**Change score Mean (SD) †**	**SRM ‡**
SF Vitality	**0**-100	35.7 (21.5)	34.1 (23.1)	-1.62 (20.2)	-0.08
FSI Severity	0-**10**	5.48 (2.07)	4.98 (2.21)	-0.50 (2.40)	0.21
FSI Interference	0-**10**	4.70 (2.37)	3.86 (2.50)	-0.84 (2.19)	-0.38
FSI Duration	0-**7**	3.46 (2.09)	3.28 (2.14)	-0.18 (2.33)	-0.08
PHQ Fatigue Item	0-**3**	2.07 (0.92)	2.07 (0.93)	0.0 (1.14)	0.0

* **Bolded** number represents **worst** score

† Change score = 6 month score – 1 month score

- For all FSI scales and PHQ fatigue item, higher scores indicate worse fatigue and negative change scores indicate improvement.
- ‡ Standardized response mean (SRM) = mean change score/SD of change scores

Table 5

Correlation Matrix at 1 Month (n = 68) and 6 Months (N = 96)

Fatigue Scale -- 1 month -- 6 months	SF Vitality	FSI Severity	FSI Interfere	FSI Duration	PHQ Fatigue
Vitality Scale		-.70 -.68	-.77 -.71	-.75 -.71	-.78 -.75
FSI Severity			.83 .78	.70 .74	.67 .62
FSI Interference				.81 .79	.72 .65
FSI Duration					.74 .70
PHQ Fatigue					

(Krebs et al., 2009; Löwe, Kroenke, Herzog, & Gräfe, 2004). Mean change scores were derived by subtracting the 1-month mean score from the 6-month mean score; then this value was divided by the standard deviation of the change score. Frequency distributions of the SRMs were similar and approximated a bell shape for each fatigue measure, albeit with a positive skew (Figure 3).

The findings from this measurement validation analysis support the use of the vitality scale to measure fatigue in the INCPAD cancer sample for the main analysis. The vitality scale performed similarly to a longer multidimensional scale (i.e., the FSI) that was developed specifically to assess cancer-related fatigue and validated in multiple cancer samples. The vitality scale's strong correlation with both the FSI and with the PHQ-15 fatigue item support its construct validity. Moreover, it demonstrated sensitivity to longitudinal change that was similar to that of the FSI.

*Depression Subscale (SCL-20) of the Hopkins Symptom Checklist (SCL-90)***.** The SCL-20 was the primary outcome measure for depression in the INCPAD study and one of three depression scales used in the current study. The SCL-20 is a modified subscale of the SCL-90 that was chosen for its demonstrated sensitivity in detecting differences in depression severity between treatment groups in previous trials (Kroenke, West et al., 2001; Unutzer et al., 2002). The 20 items ask respondents to rate how much distress was

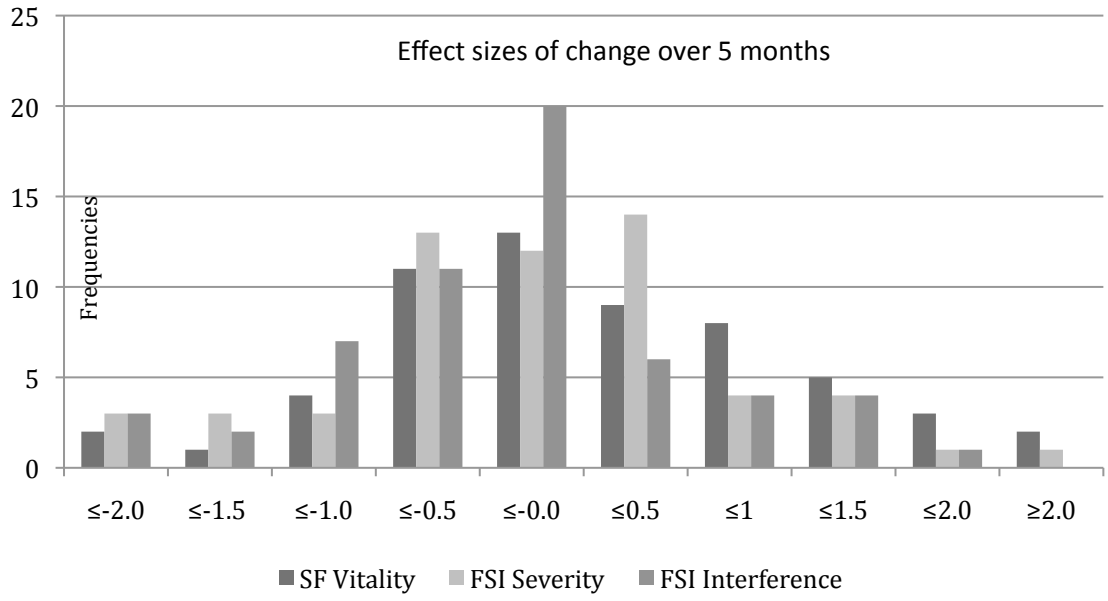

Figure 3. Comparison of change scores (standardized response means; SRMs) of the SF-36 vitality scale and the severity and interference subscales of the FSI at 1-month and 6-month assessment. (SRMs = mean change score/SD of change scores.)

experienced over the past 4 weeks because of various symptoms such as "feeling lonely or blue," "feeling no interest in things," "trouble falling asleep," and "thinking, speaking, and moving at a slower pace." For each item, five response choices range from "not at all" to "extremely."

The SCL-20 is well validated. In several studies of varied patient populations, correlations between the depression subscale of the SCL-90-R and the Beck Depression Inventory ranged from 0.73 to 0.80. The diagnostic utility of the SCL-90-R has also been demonstrated in several studies (Derogatis, 1994). In INCPAD, Cronbach's coefficient alpha was 0.89.

Patient Health Questionnaire, Depression (PHQ-9). The PHQ-9 is the depression module of the full Patient Health Questionnaire, a self-administered diagnostic instrument for common mental disorders developed for use in primary care settings (Kroenke, Spitzer et al., 2001a). Its nine depression items comprise the nine criteria upon which the diagnosis of depressive orders is based (*Diagnostic and Statistical Manual of*

Mental Disorders, 4th Edition Text Revision, 2000). In 2 studies including 6,000 patients, the PHQ-9 performed well as a brief measure of depression severity and showed good construct and criterion validity (Kroenke, Spitzer et al., 2001a). It has been recognized as a dual-purpose instrument for making diagnoses and assessing severity.

When administering the PHQ-9, interviewers ask respondents whether they have been bothered by a specified symptom over the last 2 weeks. Examples of symptoms are "little interest or pleasure in doing things," and "feeling bad about yourself, feeling that you are a failure, or feeling that you have let yourself or your family down." If the response is yes, then participants are asked whether they were bothered "several days," "more than half the days." or "nearly every day." Cronbach's coefficient alpha for the PHQ-9 in the INCPAD sample is 0.81.

Mental Health Inventory (MHI-3). The MHI-3 is a depression subscale of the Mental Health Inventory-5, which in turn is part of the SF-36 Health Survey. The MHI-3 recently has been validated as a measure for depression (Cuijpers, Smits, Donker, ten Have, & de Graeff, 2009; Rumpf, Meyer, Hapke, & John, 2001; Yamazaki, Fukuhara, & Green, 2005). The MHI-5 consists of 5 items from the SF-36 and assesses mental health (Rumpf et al., 2001). It has been tested in a large sample of the general population (n = 4,036) for its ability to screen for various mental disorders, especially depression and anxiety. It performed best in detecting depressive disorders, with sensitivity and specificity statistics comparable to 9 lengthier instruments used in primary care. More recently, Cuijpers and colleagues (2009) undertook ROC analysis and found no difference between the MHI-5 and the MHI-3 in detecting major depression and dysthymia. The MHI-3 items ask "How much of the time during the last month have you: 1.) felt downhearted and depressed?, 2.) been happy? and 3.) felt so down in the dumps that nothing could cheer you up?" Respondents choose from 5 options ranging from "none of the time" to "all of the time." Cronbach's alpha for the MHI-3 in the INCPAD sample was 0.77.

Analysis

Cross-lagged panel analysis, a structural equation modeling technique, was used to test the hypotheses. As a way of ameliorating measurement error—a common threat to validity in causal analysis—a latent variable approach was used (Shadish, Cook, & Campbell, 2002). Panel data consists of at least two variables measured at two or more time-points in the same set of subjects. Analysis of panel data has been recognized for its advantages in testing for causal effects because it can provide evidence regarding all three conditions of causality: 1) covariation of the 2 variables; 2) time precedence of the causal variable; 3) and nonspuriousness (i.e., the association of the 2 variables must not be produced by a joint association with a third variable or set of variables) (Finkel, 1995). A cross-lagged model is also a basic approach for estimating possible reciprocal effects. It provides the means to address the question: "Which is the more important influence, depression (D) on fatigue (F), or fatigue on depression?" (Greenberg, 2008).

Figure 4 illustrates the model for the main analysis. It incorporates a linear structural equation for a continuous dependent variable fatigue (F) at 3 months (T2). The equation included depression (D) at baseline (T1) and T2, and F at T1. The intervention group assignment was entered into the equation as a control variable.

The model comprises two portions—measurement and structural. The *measurement model* is made up of the observed variables (boxes in the model), which serve as indicators for the latent, or unobserved, variables (circles in the model). Unidirectional arrows from the latent variables to the indicators represent factor loadings. The *structural model* includes the latent variables and specifies the hypothesized pattern of causal influence. Straight unidirectional arrows between latent variables represent specified causal pathways, and two-headed arrows represent covariance (unanalyzed in the case of exogenous variables), or in the standardized solution, correlations. Error terms, also called disturbances, are represented by arrows coming into the variables from an unmodeled source.

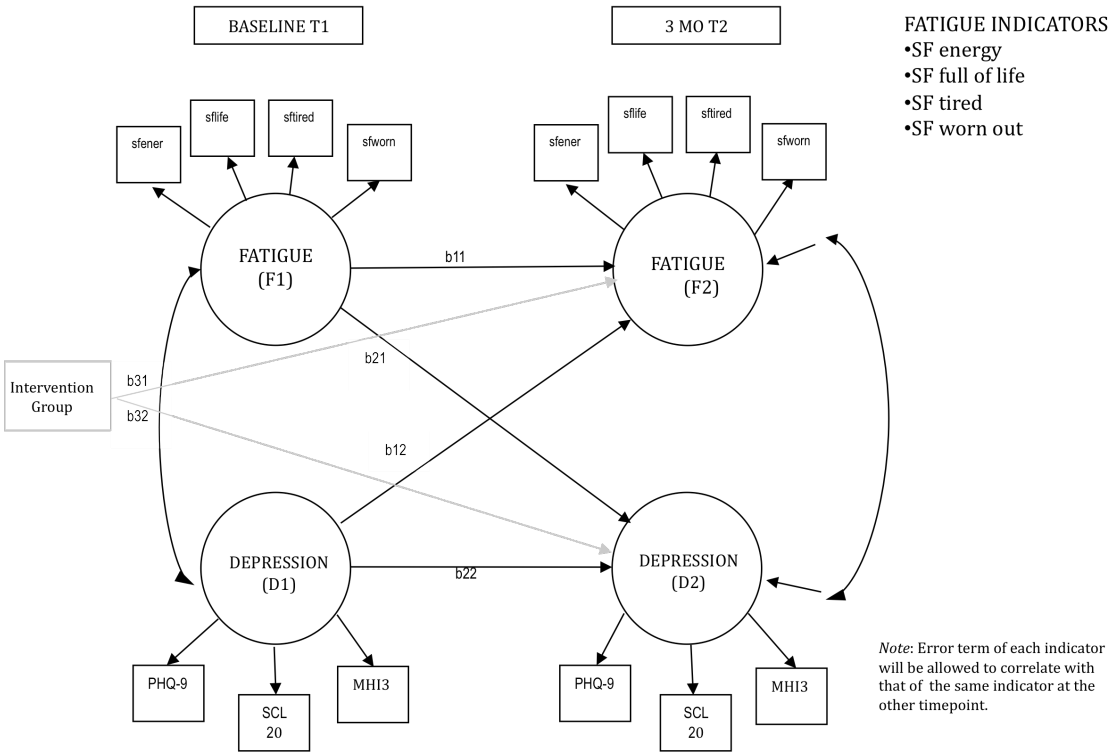

Figure 4. Latent variable cross-lagged panel model of the relationship of depression and cancer-related fatigue.

Measurement Model

Specification of the indicators for the latent variables fatigue and depression was carefully considered so as to minimize the potential for measurement error. For depression, instrument sum scores were used as indicators, whereas for fatigue, individual items serve as the indicators. Little, Cunningham, Shahar, and Widaman (2002) extolled the utility of using intact scales with established norms and psychometric properties as indicators of a latent construct. Their endorsement of entering scores from such scales in their original untransformed metric provided the basis for the specification of the depression measurement model, as the validity of all three instruments used in the INCPAD study for measuring depression has been empirically established. The use of three indicators can be considered a strength, as it renders the latent construct of depression as locally "just-identified." This means that the number of parameters and observations is equal (Kline, 2005) and therefore a single unique solution exists that

optimally captures the relations among the items. Little and colleagues (2002) argue that just-identification is ideal for the measurement of a latent construct in a structural equation model.

For fatigue indicators, items were considered individually rather than at the scale-total level primarily because the INCPAD study included only one fatigue scale, as the study was not designed with fatigue as an intended primary outcome. Aside from fatigue items embedded in the depression instruments, available fatigue-related items in the INCPAD questionnaire included the four that make up the vitality scale and a single item from the PHQ-15 Somatic Symptom Scale discussed in the Measures section. The latter was ruled out as an indicator because data seriously violated the normality assumption of SEM. Responses were on a 3-point scale, and at baseline, 319 respondents (79%) endorsed the choice representing the *most* bother from fatigue, making for a highly negatively skewed distribution. With only the vitality scale remaining, use of the total score as a single indicator would be less than ideal, as multiple measures of a latent construct reduce the effects of measurement error (Kline, 2005). Thus, the 4 items of the vitality scale were used as indicators for fatigue.

Structural Model

The model was specified according to convention in cross-lagged panel data (Finkel, 1995; Greenberg, 2008; Kessler & Greenberg, 1981; Shadish et al., 2002). The structural pathways between F1 and F2 (fatigue) and between D1 and D2 (depression) serve to adjust each 3-month variable for its corresponding baseline level; therefore the 3-month variables represent residualized change scores. A significant correlation for the pathway (b12) from D1 to F2 would lend support to hypothesis 1. A significant correlation for pathway (b21) from F1 to D2 would lend support for hypothesis 2 provided that the magnitude is lower than for b12. The INCPAD intervention group assignment is modeled as a single-indicator latent variable in the model.

Statistical Analysis

The analysis was conducted with maximum likelihood estimation using LISREL 8.8 (Jöreskog & Sörbom, 2008). Evaluation of the hypothesized model fit included a measurement phase and a structural phase. In SEM, a variance-covariance matrix is generated from observed data. Factor analysis is used to confirm the measurement model that defines the latent variables. The structural phase involves a path-analysis approach, in which the SEM program determines estimates that will most nearly reproduce the variance-covariance matrix. The program finds estimates for each parameter that are most likely to reproduce the observed path beta coefficients while simultaneously taking into account the most likely possible reproduction of all the other correlations in the input matrix. Kline's (2005) outline of steps for completing an SEM analysis guided both stages of the analysis, including detailed data preparation and screening. Major steps included evaluating model fit, interpreting the parameter estimates, and considering equivalent models. In SEM, if the initial structural model does not fit the data well, it may be re-specified and re-evaluated before continuing with the interpretation of estimates.

SEM program output includes various fit indices that allow the investigator to statistically assess whether and how well the observed model fit the hypothesized model (Klem, 2000). For the current study, fit indices selected *a priori* to determine goodness-of-fit included indices of absolute fit, the chi-square statistic (χ^2) and the Standardized Root Mean Squared Residual (SRMR); a parsimonious fit index, the Root Mean Square Error of Approximation (RMSEA); and an incremental fit index, the Comparative Fit Index (CFI) (Hu & Bentler, 1999; Weston, Gore, Chan, & Catalano, 2008). Guidelines for interpreting the indices and cutoff scores for the current study are at Table 6.

Power Analysis

SEM is generally understood among statisticians to require large samples, with 200 being the suggested minimum threshold (Barrett, 2007; Kline, 2005). Increasingly complex models require larger samples, and certain estimation methods require very

Table 6

Fit Indices and Cutoffs for the Current Study

Index (Range)	Guidelines for interpretation	Cutoff
Chi Square (χ^2)	Nonsignificant χ^2 suggests the model fits the data (i.e., differences non-significant). Usually significant in larger samples.	> 0.05
Standardized Root Mean Square Residual (SRMR; 0 - ∞)	0 = perfect fit. Values lower than 0.06 indicate good fit	< 0.06
Root Mean Square Error of Approximation (RMSEA; 0 - ∞)	0 = perfect fit; suggested cutoff is 0.05	< 0.05
Comparative Fit Index (CFI; 0 - 1)	Values closer to 1 indicate better fitting model; suggested cutoff is 0.95	> 0.95

Sources: Hu & Bentler (1999); Weston, Gore, Chan, and Catalano (2008)

large numbers. For path analysis, Kline made a general recommendation to have a ratio of participants to free parameters at 20:1, although he allowed that 10:1 may be a more realistic target. If the ratio falls below 5:1, the statistical analysis is in doubt, according to Kline's rules of thumb. The hypothesized path model for the proposed study has 37 parameters to be estimated; therefore it requires 185 cases to be considered viable according to these guidelines. The main analysis was ultimately run only with cases with no missing data, leaving a sample size of 329, which fell short of the recommended numbers but well exceeds the lower threshold of acceptability.

Alpha was set at .05, 2-tailed. Kline (2005) noted that statistical significance testing is less central in SEM than in many conventional data analysis techniques, partly because of the difficulty securing large enough sample sizes to detect significant effects. More than that, however, in SEM the focus tends to be on the evaluation of entire models and the fit statistics, with the big-picture view taking precedence over attention to individual effects.

RESULTS

The data were screened relative to the assumptions of SEM procedures (Kline, 2005; Tabachnick & Fidell, 2000) using SPSS (PASW) 17 statistical software. For each variable of the main model, range values, means, and standard deviations (SDs) were inspected for plausibility. Univariate outliers were identified through box plots and examined. Two cases that were more than 3.5 SDs beyond the mean on the SF energy variable were adjusted to 0.5 above the next highest value, thus keeping the scores in the analysis but reducing the potential for distortion of the distribution. Scatter plots for the depression scales were examined for multivariate outliers as a way of confirming assumptions of linearity and homoscedasticity. An examination of a single extreme case revealed it to have a low baseline PHQ-9 score while the other depression scales were very high, along with other incongruities in the data. The score for the baseline PHQ-9 was deleted for that case. Mahalanobis distance statistics were reviewed in search of multivariate outliers. As a result, three cases were examined for incongruity among the scores but none were found to be extreme. No adjustments were made based on the Mahalanobis distance statistics. Each distribution was evaluated for normality by examining histograms and statistics for skewness and kurtosis. Depression scales consistently approximated a normal distribution. The vitality scale item distributions roughly resembled normal but were positively skewed. None had skewness or kurtosis values exceeding the absolute value of 1, however, suggesting each was within the range of a normal distribution (Mertler & Vannatta, 2005). The conclusion of this assessment was that deviations from normality were insubstantial so that standard SEM analysis and fit indices were used. The assumption of multicollinearity was checked by reviewing the squared multiple correlations between each key variable and the others, reported in the

LISREL output. In no case did the statistic exceed 0.90, which is the cutoff suggested by Kline (2005).

The sample size was reduced to 329 for the main analysis because the SEM procedure would not converge using the full dataset (N = 405). The problem was resolved by using only cases with full data, an approach recommended by Kenny and Harackiewicz (1979) for cross-lagged panel analysis. Cases that were not assessed at 3 months (17% of the sample) accounted for a large proportion of the missing data. At the time their 3-month assessment was due, 16 participants had died, 24 had dropped out, and the research team was unable to make contact with 30 (see flowchart, Figure 2). Baseline characteristics of the 329 participants who were included in the current analysis were compared to those of the full INCPAD sample using T-tests or Z-tests for proportions. No significant differences were found between the groups for age, gender, race, education, marital or employment status, income, type or phase of cancer, number of comorbid diseases, disability, or mean scores for fatigue, pain, depression, or quality of life (see Table 2).

Bivariate correlations, means, and SDs are presented for the fatigue measures and separately for the depression measures in Table 7. A table with correlations across all variables at both time-points can be found at Appendix C. Magnitudes in the latter table ranged from 0.24 to 0.85. All correlations were significant and in the expected direction. Values between fatigue and depression were negative; however, this suggested a positive association as expected because higher vitality scores suggest less fatigue whereas higher depression scores suggest worse symptoms. Visual inspection revealed that intercorrelations among the depression scales tended to be higher than those among the fatigue items. At baseline, depression scale correlations ranged from 0.65 to 0.74 and at 3 months from 0.73 to .85. For fatigue, baseline correlations ranged from 0.29 to 0.74 and at 3 months from 0.45 to 0.78, with the strongest association being between the two items referring to feeling tired and feeling worn out.

Table 7

Bivariate Correlations, Means, and SDs for Fatigue and Depression

Fatigue

Variable	1	2	3	4	*M*	*SD*
1. SF energy	—	.41	.48	.49	1.90	0.88
2. SF life	.53	—	.29	.35	2.40	1.15
3. SF worn	.53	.49	—	.74	2.29	1.06
4. SF tire	.56	.45	.78	—	2.06	0.99
M	2.19	2.58	2.65	2.44		
SD	1.03	1.22	1.13	1.08		

Depression

Variable	1	2	3	*M*	*SD*
1. PHQ-9	—	.74	.65	12.84	6.85
2. SCL-20	.85	—	.74	1.44	0.73
3. MHI-3	.73	.76	—	8.05	2.96
M	9.20	1.10	7.26		
SD	6.28	0.69	3.02		

Note. N = 329. Intercorrelations for Time 1 are presented above the diagonal, and intercorrelations for Time 2 are presented below the diagonal. Means and SDs for Time 1 are presented in the vertical columns, and means and SDs for Time 2 are presented in the horizontal rows. For fatigue measures, higher scores indicate greater vitality. For depression scales, higher scores indicate more depression. From the SF vitality scale: SF energy = "How much of the time during the past 4 weeks…did you have a lot of energy?" SF life = "…have you felt full of life?" SF worn = "…did you feel worn out?" SF tire = "…did you feel tired?" PHQ-9 = Patient Health Questionnaire, Depression, SCL-20 = Depression Subscale of the Hopkins Symptom Checklist, MHI-3 = Mental Health Inventory Depression Subscale.

All correlations are significant at the 0.01 level (2-tailed).

As for the cross-sectional correlation of fatigue with depression, the total for the SF vitality scale score at baseline was found to have relatively strong and significant correlations with all three depression scales. For the PHQ-9, r = -0.49, for the SCL-20, r = -0.62, and for the MHI-3, r = -0.54, with negative correlations indicating that greater depression was associated with less vitality/greater fatigue.

Measurement of Fatigue and Depression

Prior to testing the causal model, the measurement model was examined through a confirmatory factor analysis (CFA) to increase confidence that the specified indicators for depression and fatigue were indeed capturing separate constructs in the sample data. First, the model was tested using baseline data with latent factors of fatigue and depression each being assigned the respective indicators, and with the latent factors being allowed to correlate freely. The standardized correlation of fatigue and depression was 0.76. Factor loadings were consistently strong (range of standardized estimated correlations for fatigue indicators was -0.58 to -0.69; for depression indicators, 0.78 to 0.94) and all model indices suggested good fit χ^2 (11, N = 329) = 17.72 (p = 0.08), SRMR = 0.031, RMSEA = 0.043, and CFI = 1.00. To further confirm the existence of two factors, a second model was analyzed for comparison in which the correlation between the latent factors was fixed to equal 1.0, thereby rendering the two factors as identical—essentially equivalent to replacing the two factors with one (Kline, 2005). Relative fit of the two models was tested with the chi-square difference test. The fit of two models was found to differ significantly, χ^2 (1, N = 329) = 54.37 (p < .005) with the two-factor model having superior fit. The tests were repeated with 3-month data with a similar outcome. Results suggested that the indicators selected for the causal analysis were capturing two distinct factors in the data as intended.

Structural Analysis of Panel Data

The aim of the current study was to examine whether depression exerts causal influence on fatigue over time in cancer patients and whether reciprocal effects exist. Both hypotheses—that depression would predict changes in fatigue over 3 months and that reciprocal effects would exist but would be of lower magnitude—were evaluated in the same analysis of panel data. The model was specified as has already been presented in Figure 4.

In an effort to avoid error due to omitted predictors, several variables were tested as potential control variables. Age, gender, cancer type, and cancer phase were evaluated as potential confounders, along with other variables that have been found in previous research to be associated with CRF. Baseline bivariate correlations for cancer type, cancer phase, anxiety, pain, sleep quality, shortness of breath, and activity were reviewed—some of which were measured in the INCPAD study with standardized scales and others of which were measured with one or two items. The range of magnitude of correlations with fatigue was 0.02 to 0.36; the range of magnitude of correlation with depression was 0.04 to 0.43. Although some of the baseline bivariate correlations were relatively small in magnitude, each variable had a statistically significant correlation either with fatigue items or depression scales or both. Tests were run to see if including each baseline variable in the model would have a significant effect on fatigue or depression at the second time-point. No significant effects were found; therefore, no control variables were included in the main analysis except the intervention arm, which had been included in the hypothesized model.

The initial analysis with the *a priori* model specified as planned (Figure 4) did not show adequate fit, χ^2 (76, N = 329) = 279.21, ($p < 0.001$), SRMR = 0.073, RMSEA = 0.09, and CFI = 0.97. Examination of the Lagrange multiplier modification indices, however, suggested that allowing the "full of life" fatigue indicator to cross-load on depression at each time point would reduce χ^2 , thereby improving fit. This item from the SF vitality scale asks "How much of the time during the past 4 weeks have you felt full of life?" Because it is conceptually plausible that this item would provide information relevant to both depression and fatigue (see further discussion later), a new model was

created with parameters freed from latent depression to the sflife indicator at each time point. Eight correlations between error terms were also freed based on modification indices, after determining the conceptual reasonableness of each change. Parameters were freed to allow item error terms to correlate between "tired" and "wornout" items and between "full of life" and "a lot of energy" at each time point. Further, the "full of life" error terms were allowed to correlate with the MHI-3 error terms.

The revised model achieved good fit, as demonstrated by three of the four fit indices selected *a priori*: χ^2 (66, N = 329) = 88.16, p = 0.04, SRMR = 0.030, RMSEA = 0.032, and CFI = 1. Although the significance of χ^2 suggests the data failed an absolute-fit test, this finding is expected since an exact fit is a rare occurrence, especially in larger samples (Weston et al., 2008). Kline (2005) advised that over-reliance on χ^2 as a fit index may lead to rejection of models with reasonably good fit.

Because the new measurement model fit the data well, it was used for the causal analysis. Although statistically suggested modifications were made *post hoc*—a procedure that has been challenged by some in the SEM literature (Kline, 2005; Weston et al., 2008)—the changes were conceptually reasonable and were deemed to be minor relative to the overall model structure.

The main findings are presented in Figure 5. The cross-lagged structural path from baseline depression to fatigue at 3 months was nonsignificant (standardized β = 0.01, z = 0.10) suggesting that baseline depression had no causal influence on change in fatigue after 3 months. Likewise, the structural path from baseline fatigue to depression at 3 months was nonsignificant (standardized β = 0.10, z = 1.07). Neither of the study hypotheses was supported by these results. Results for the structural paths from the intervention group control variable lent additional support for the validity of the model. A significant positive effect was found on change in depression at 3 months for membership in the intervention arm of the study (standardized β = 0.20, z = 4.35), showing that the depression intervention predicted less depression at Time 2. No effect of the intervention was found for fatigue, however, as the structural path from the intervention control variable to fatigue was nonsignficant (standardized β = 0.09, z = 1.61).

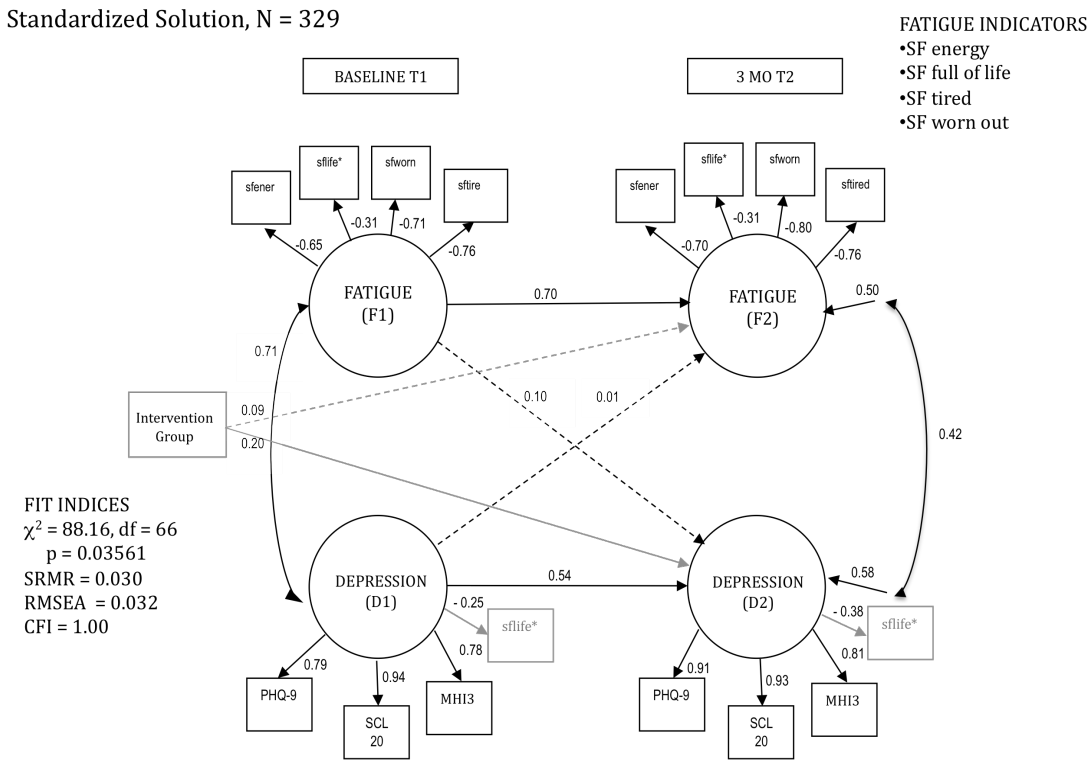

Figure 5. INCPAD cross-lagged panel model. *Shaded indicator (sflife) is a crossloading item. Values for unidirectional arrows (structural paths) are standardized regression coefficients; values associated with bidirectional arrows are Pearson correlation coefficients. Paths with significant coefficients are solid; nonsignificant paths are dashed. Shading indicates a control variable (i.e., Intervention Group). Loadings of fatigue indicators are negative because higher observed scores suggest lower fatigue (sftired and sfwornout scores were reversed). $p < 0.05$.

A critical structural assumption that must be met in order for a cross-lagged panel analysis to be valid as a test of causal influence is that of stationarity, the requirement that the correlations between fatigue and depression are equal at both time points (Kenny & Harackiewicz, 1979). To set conditions conducive to stationarity, the variables to be tested in cross-lagged analysis should be correlated at a moderate to large magnitude—at least 0.30. In the current main analysis, the unstandardized correlation of fatigue with depression was 0.71 at time 1 and 0.78 at time 2. In order to insure the difference was nonsignificant, an alternate model was created with the correlations between the synchronous latent variables constrained to be equal. The fit indices of this model were then compared to the main model, which had no such constraint. The indices were nearly

identical. Indices for the constrained model were χ^2 (66, N = 329) = 88.72, p = 0.04, SRMR = 0.03, RMSEA = 0.03, and CFI = 1.00. A χ^2 difference test was nonsignificant, $\Delta\chi^2_{(1,0,\, N=329)} = 0.56$, p = 0.45, indicating that the models were not significantly different; thus the assumption of stationarity was met.

An alternative model was evaluated to explore the consequences of reducing obvious measurement overlap between fatigue and depression. Because fatigue is a core symptom of depressive disorders, measurement overlap exists in many multi-item self-report depression scales (Brown & Kroenke, 2009; Jacobsen et al., 2003). As has already been mentioned, previous researchers seeking to understand the relationships between the two symptoms have attempted to address this either by choosing depression instruments that focus exclusively on mood symptoms or by comparing relationships of the two constructs with and without fatigue-related items included in multidimensional depression scales. Two of the depression indicators in the current study contain items assessing fatigue symptoms. The SCL-20 asks how much distress had been caused by "feeling low in energy or slowed down" and "feeling everything is an effort." The PHQ-9 asks about being bothered by "feeling tired or having little energy." An alternative dataset was prepared with these items dropped from the depression scales. The model was then estimated the same as in the main analysis but with the revised dataset.

Again, model indices suggested a good fit, and unlike the main model, the chi-square statistic was nonsignificant, suggesting it met the specifications for absolute fit, χ^2 (66, N = 329) = 81.67, p = 0.09, SRMR = 0.027, RMSEA = 0.044, and CFI = 1.00. The cross-lagged paths between fatigue and depression remained nonsignificant, suggesting no causal influence—consistent with the main analysis. The magnitudes of most of the structural paths in the model changed, although none by more than 0.10, as follows: D1 → D2 standardized β = 0.56; F1 → F2 standardized β = 0.69; D1 → F2, standardized β = -0.02, *ns*; F1 → D2, standardized β = -0.08, *ns.* Correlations between the latent variables at baseline were different from the main model results (-0.67 compared to -0.71 with complete measures) and again at three months (-0.39 compared to -0.42). The magnitude of effects of the intervention control remained the same. Although analyzing the model with an apparent reduction in measurement overlap did appear to improve the fit of the

model somewhat, statistical comparison could not be undertaken because the models are not nested. The structural effects did not change in any apparently meaningful way. This outcome suggests the overlap of fatigue items in the depression scales did not unduly influence the findings.

DISCUSSION

The purpose of the current study was to examine whether causal influences exist in the relationships between depression and fatigue in cancer patients. Based upon a theory that depression is a perpetuating factor of CRF, the main hypothesis held that depression would have causal influence on fatigue over time. A second hypothesis held that a reciprocal effect would be found, but that the influence of depression on changes in fatigue would be stronger than the reverse. The sample comprised 329 patients with various types of cancer and in different phases of oncology treatment or post-treatment who participated in a 12-month RCT of an intervention to treat depression and pain symptoms. Data from baseline and 3 months were analyzed for fit with a cross-lagged panel model, a statistical method that has been endorsed in the literature as an appropriate method to assess for directional causal influence. Results failed to support either of the study hypotheses. The data fit the model reasonably well; however, no evidence was found to support the hypothesis that depression had a causal influence on fatigue over three months during the course of the intervention. Furthermore, no support was found in this analysis for the hypothesis that fatigue causally influences depression over time.

The findings are supported by several strengths in study design. The fact that the majority of the sample entered the study with both elevated depression and fatigue assured appropriate range to demonstrate improvement over time. Moreover, conducting this analysis in a trial of a treatment that targeted depression increased the likelihood that depression would improve within the 3-month timeframe, a condition that is ideal for an evaluation of causal influence of this nature. The findings replicated those of the INCPAD trial suggesting that the depression-and-pain intervention had positive effects for depression compared to the usual care control group. Fatigue, however, was not significantly affected by intervention group membership, according to the panel analysis.

The sample of 329 was sufficient to support the analysis. Measurement was found to be adequate in the confirmatory factor analysis step. That taken together with the fact that latent variable SEM accounts for measurement error suggests that the validity of these findings may be less threatened by measurement error than are many studies using other statistical approaches.

These findings make an important contribution to what is currently understood about the interrelationship of depression and CRF. Although a strong correlation between depression and CRF has been well established in previous research, far too few longitudinal studies have been undertaken and little is known about causal influences. Only a few studies have attempted to evaluate whether these symptoms tend to change together or independently over time, and the results have been mixed and inconclusive. A comprehensive search of the literature revealed none that had employed structural equation modeling, an advanced technique in causal analysis.

Although the number of studies that have analyzed the causal relationship between CRF and depression are few and results are mixed, the current findings are consistent with the majority of the published longitudinal studies in this domain. Perhaps the one with the most notable similarities in findings is a randomized, double-blind controlled trial of paroxetine to treat fatigue in patients ($N = 479$) undergoing chemotherapy for the first time (Morrow et al., 2003). As in the current study, participants with a variety of types of cancer were recruited from multiple oncology sites and pharmacological treatments were featured. A key difference is that in the Morrow and colleagues trial, fatigue was the symptom that was targeted, whereas the INCPAD trial targeted depression and pain. Another important distinction is found in the way the hypotheses were conceptualized, as the study by Morrow and colleagues tested whether the two symptoms share a common etiology. Instead of conceptualizing depression as a perpetuating factor, Morrow and colleagues had hypothesized that fatigue and depression share a common neural pathway involving serotonin. However, they found that paroxetine, a selective serotonin reuptake inhibitor, reduced symptoms of depression within 3 weeks but had no effect on fatigue at either of two follow-up assessments at cycles 3 and 4 of chemotherapy. As in the current study, these investigators found that

although depression and fatigue were strongly correlated in the sample, only depression was affected by the intervention.

The current findings are also consistent with those of Visser and Smets (1998), who studied fatigue, depression, and QoL by interviewing a heterogeneous sample of 250 cancer patients a week before beginning radiation therapy, 2 weeks after treatment, and 9 months later. One of the stated aims of their study was to investigate the cause-and-effect relation between fatigue and depression. Because correlations have been found to be so high, investigators expected fatigue and depressive mood to follow a similar course over time, but instead each exhibited independent patterns of change. In four other studies that used smaller samples of patients with specific cancer types currently receiving treatment, researchers reported findings about the longitudinal relations of fatigue and depression that could be interpreted to suggest that the two symptoms change (or fail to change) independently over time (Geinitz et al., 2001; Pirl, 2008; Schumacher et al., 2002; Stone, Hardy et al., 2000).

One of these groups of investigators, Stone and colleagues, reported findings from a different study that could be taken to suggest that the two symptoms may tend to change together. They evaluated depression, fatigue, and other symptoms occurring as treatment-emergent side effects in breast or prostate cancer patients ($N = 69$) who were assessed before and after radiation therapy (Stone et al., 2001). In their study, small but significant increases in depression scores were associated with small increases in fatigue scores. This research differed from the current one in that it focused on fatigue increases relating to radiation therapy and there was no treatment for either depression or fatigue involved. It is plausible that a cytotoxic treatment such as radiation therapy can have several side effects that differ in etiology, in which case the simultaneous increases in both fatigue and depression were not causally related but due to different mechanisms.

Only one other study ($N = 250$) reported finding a longitudinal relationship in change in depression and fatigue (Tchekmedyian et al., 2003). This was a secondary analysis of data from a randomized, double-blind, placebo-controlled trial of darbepoetin alfa to treat anemia in lung cancer patients. The study was conceived as a test of whether improvements in fatigue would predict improvements in the distress of depression and

anxiety. Assessment of fatigue, anxiety, and depression occurred at baseline and between weeks 4 and 12. Improvements in fatigue were associated with reductions in both depression and anxiety. In multiple regression, for each unit of improvement in the fatigue score, there was a corresponding improvement of 0.7 units in anxiety and 0.8 units in depression levels. Although the Tchekmedyian and colleagues study findings suggest a causal influence between fatigue and depression, there are differences in design from the current study that are important. It is possible that the fatigue associated with anemia is different from non-anemic CRF. For one thing, anemia has been established as a "treatable contributing factor" of CRF and has a pharmacologic treatment that is known to be helpful (Berger et al., 2009). The Tchekmedyian study sample was made up of lung cancer patients with anemia (hemoglobin ≤ 11 g/dL) and receiving cyclic platinum-containing chemotherapy. In the current study, only 18% of participants were lung cancer patients and 44% were in maintenance or disease-free status. Anemia was neither assessed nor treated. These differences may account for the differences in findings of the current study and the previous study.

Overall, in terms of the few relevant longitudinal studies that have been found in the literature, none directly contradicted the current study. Six of the longitudinal studies failed to support a causal influence between depression and fatigue in either direction; only two found a relationship between change in fatigue and change in depression and both were substantially different from the current study both in aims and design.

Implications

Theory

The current study adds new data to the evidence regarding the three unanswered questions about CRF that were posed by Jacobsen et al. (2003) and discussed in the background (p. 14): first, to what degree do fatigue and depression conceptually differ; second, to what degree to they co-occur; and, third, are there causal relationships?

Regarding the first question, the current findings—both the measurement model and the structural model—are consistent with the theory that depression and fatigue are two distinct entities in the cancer context. This matter may have been previously settled (Skapanakis, Lewis, & Mavreas, 2004; Visser & Smets, 1998), but the high correlations of fatigue and depression and their overlap in multidimensional measurement and syndrome-based diagnoses continue to blur the boundaries between the two symptoms. Reuter and Härter (2004), for example, published a conceptual paper positing that when accompanied by a depressive disorder in cancer, fatigue is subsumed by the depression symptom complex. They concluded that the question of diagnostic independence remains unanswered and expressed the hope that certain antidepressant medications might help with CRF. One could point to the cross-loading of one of the SF vitality scale items in the current study—the "full of life" item—as an example of a blurring of the distinction. This item has been validated to measure respondents' status on an energy/fatigue continuum. In our measurement model, SF life loaded adequately on the latent fatigue variable. In the full panel model, however, the indicator statistically cross-loaded onto the latent variable for depression. Developers of the SF-36 have written about the difficulties they experienced in developing a scale for energy/fatigue. There had been no agreement among experts on how to define it. These authors considered it to be an aspect of both physical and mental health. The difficulty, they wrote, was in developing a measure of energy/fatigue that would be conceptually and empirically distinct from "similar concepts such as depression, positive affect, cognitive functioning, and sleep problems" (Stewart, Hays, & Ware, 1992, p. 147). In the final result, the "full of life" item was paired with the "a lot of energy" item to cover the energy side of the continuum. For our study with cancer patients, it was considered conceptually reasonable that responses to an item asking about feeling "full of life" would provide information about both depression and fatigue, so the item was allowed to cross-load in our model, thereby improving the fit. Like the inclusion of fatigue items as core symptoms in many depression scales, this "full of life" item from a fatigue scale cross-loading on depression is another example of the blurring of the conceptual distinction between depression and fatigue.

Yet when taken as a whole, results of the current study lend support to depression and fatigue existing as distinct entities. If the two were actually one, we would expect the CFA model with the two variables constrained to be equal to have the best empirical fit; yet that was not the case. Even more compelling, however, is the differential response to the intervention that specifically targeted depression and pain but not fatigue. For one thing, intervention arm membership had a significant effect on change in 3-month depression while it had no demonstrated effect on change in fatigue. Besides that, the stability path of the fatigue variable over the 3 months was of higher magnitude than that of depression; in other words, depression changed more than fatigue did.

In writing about fatigue in the context of MDD and medical disorders including but not exclusive to cancer, Arnold (2008) noted that fatigue is commonly a residual symptom in depressed patients who respond to antidepressants. She hypothesized that fatigue may involve neuronal circuits distinct from those that influence depressed mood. She encouraged studies of pharmacological treatments that specifically target fatigue within the context of MDD. The findings of the current study could be considered to be consistent with these ideas.

As for the second question posed above about co-occurrence of CRF and depression, the current findings lend still further support to the well-established recognition of a strong association. The correlations in our relatively large sample of patients with various types of cancer were strong at baseline, and although the magnitude of the association between fatigue and depression declined over time as depression improved and fatigue did not, the correlation remained strong throughout.

Regarding the third question about the existence of causal relationships, it has already been emphasized that our study found no support for a causal relationship between the two symptoms in either direction. That leaves us to ponder a scenario in which two distinct symptoms occur together frequently in the cancer context but may have no causal relationship. Without a causal connection, to what might we attribute the strong correlation of occurrence?

As has been pointed out by previous researchers (Jacobsen et al., 2003), there may be a third factor that causes *both* fatigue and depression, or, more likely, multiple causes

that are common to both fatigue and depression in the cancer context. Numerous possible common causes have been advanced speculatively: for example, certain forms of cancer treatment such as biological response modifiers, increased levels of proinflammatory cytokines that occur as a result of cancer treatment, and certain types of cancer such as pancreatic (Fann et al., 2008; Jacobsen et al., 2003). A related but slightly different idea was formulated by Skapinakis and colleagues (2004) who speculated about possible explanations for the magnitude of longitudinal associations between depression and unexplained fatigue (not necessarily in cancer). These authors spoke of the possibility that fatigue and depression could be independent risk factors for each other in a manner resembling "an etiological vicious cycle." A possible mechanism, they speculated, could be level of physical activity, which may decline in the context of either depression or fatigue. Physical activity is known to have a protective effect in depression, and deconditioning is believed to be important in the development of unexplained fatigue. These factors could interact in a complex way to exacerbate unexplained fatigue, or in the case of cancer, persistent cancer-related fatigue. Yet in such a scenario, one would expect the hypotheses of the current study to have been at least partially supported.

The most plausible explanation for the findings of the current study may be the existence of a variable or, more likely, multiple variables that were not specified in the main model but that have a causal influence on levels of both fatigue and depression. It is quite likely that the cancer context comprises multiple factors that act as common causes to both depression and fatigue, which interact in complex ways to yield the strong associations such as those found in the INCPAD sample.

Practice

The current findings failed to support the perpetuating factors model presented in the background section that suggested that improvements in a cancer patient's depression would lead to improvements in CRF. Rather, the practical implication of the current study is that treating depression may *not* be helpful in treating fatigue. This is consistent with NCCN treatment guidelines for CRF, which categorically state that antidepressants

are not recommended to lower fatigue (Berger et al., 2009). Two reviews of current treatments for CRF that endorsed antidepressants to treat fatigue were examined. One cited only "clinical observation" and no clinical trials to support the recommendation (Jacobsen et al., 2003); the other cited three placebo-controlled randomized trials of antidepressants that failed to improve CRF, but nevertheless recommended antidepressants as potentially helpful for fatigue if it is comorbid with depression (Escalante, 2010). The current study adds to an extant body of literature that suggests antidepressants are not helpful in treating fatigue, whether or not comorbid depression is present. No empirical studies were found that contradict this.

Instead of supporting the approach of addressing CRF through depression treatments, the current findings suggest the importance of offering patients treatments that are specifically developed to target fatigue. This will require the focused attention of cancer care researchers as no gold standard of treatment has yet been established (Kangas, Bovbjerg, & Montgomery, 2008). Outside of the context of anemia, pharmacological treatments for CRF are in investigational stages. Psychostimulants (e.g., modafinil, which was developed for narcolepsy) may be promising and warrant more research (Berger et al., 2009); however, side effects such as restlessness, agitation, and insomnia may be especially problematic for CRF patients (Breitbart & Alici, 2008; Hanna et al., 2006).

NCCN guidelines position psychosocial and activity-based interventions as the first line of treatment for CRF (Berger et al., 2009). A systematic review of 119 studies combined with a meta-analysis of 57 RCTs concluded that both exercise and psychological interventions led to improvements in CRF. No significant differences were found between the two categories of interventions (Kangas et al., 2008). Jacobsen and colleagues (2007) conducted a systematic review and meta-analysis of 41 studies, 30 of which were RCTs, evaluating the efficacy of nonpharmacologic interventions for adult cancer patients in which fatigue was an outcome variable. The authors categorized treatments as either activity-based or psychological and rated quality indicators using criteria from the Cochrane Collaboration (Mulrow & Oxman, 1997). Activity-based treatments were exercise programs practiced either in a supervised setting or at home.

The 27 psychological interventions reviewed included group or individual cognitive-behavioral therapy, educational programs, supportive-expressive therapy, and supportive therapy. Fifty percent of psychological trials and 44% of activity-based trials that were rated fair or better in quality resulted in significant findings favoring the intervention condition. The reviewers concluded their findings provided limited support for use of nonpharmacological interventions for CRF.

Reviewers of the current evidence base for promising interventions have recommended further investigation of various categories of nonpharmacological treatment, grouped by NCCN guidelines into categories of cognitive-behavioral, behavioral , psycho-educational/educational, and supportive-expressive therapies. Both NCCN guidelines (Berger et al., 2009) and Mustian et al. (2007) support continuing investigation of nonpharmacologic behavioral interventions for CRF that include exercise, psychosocial support, stress management, energy conservation, nutritional therapy, sleep therapy, and restorative therapy. Kangas and colleagues (2008) recommended further trials of exercise and walking programs, restorative approaches, and cognitive-behavioral and supportive-expressive therapies.

Limitations

Although the current study contributes to understanding of the interrelationship of CRF with depression, several limitations must be taken into account. The use of a heterogeneous sample of cancer patients—individuals with a range of types of cancer and in various phases of treatment or survivorship—can be considered both a strength and a limitation. In its heterogeneity, the sample mimics the range of patients treated in oncology clinics, which enhances generalizability to a clinic setting. A particular strength of the INCPAD sample is that it included patients from both urban and rural centers. On the other hand, CRF may operate differently in specific types of cancer or phases of treatment, and its relationship to depression may differ accordingly. In the current study, mean scores for the vitality scale did not differ by type or phase of cancer, and neither type nor phase of cancer had a significant effect on change in fatigue or depression when

tested as potential control variables in the panel model. Sample size was insufficient, however, to afford confidence in these findings; therefore the conclusions may not apply to all types of cancer or phases of treatment.

Another limitation may be the lack of multiple well-validated fatigue scales to support the latent variable fatigue in the current analysis. Having three such scales for depression was a strength. The lack of multiple full scales for fatigue was appropriately addressed by validating the vitality scale in a comparison with the Fatigue Symptom Inventory in a subsample. That plus the acceptable performance of the fatigue indicators in the CFA phase of the analysis suggests measurement was at least adequate in this analysis.

It should also be acknowledged that it is possible that other types of treatment for depression (e.g., nonpharmacological) would have more of an effect on fatigue, both in the INCPAD study and in the other intervention trials that found no positive effects of antidepressant treatment on fatigue. The INCPAD study emphasized frequent monitoring of depression and pain, and for those who reported active symptoms, medications were recommended. Most of the treatment was pharmacological, which is similar to studies by others that have found that treating depression did not help with fatigue. Testing for effects on fatigue as a primary aim in trials of nonpharmacological treatments for depression would add to our understanding. It would be particularly interesting to see if depression treatments that tend to have broad effects on multiple symptoms such as anxiety and sleep disturbance would also help with fatigue (e.g., cognitive-behavioral therapy or acceptance- and mindfulness-based therapies).

A final issue to take into account when considering these findings is the possibility of incorrect timing of the causal lag. Difficulties with specifying measurement occasions that match actual causal lags that are finite have been noted in the literature (Kline, 2005). Although three months may be a reasonable time in which to expect antidepressant treatment to improve depression, the current study does nothing to inform us as to whether the depression improvements might lead to changes in fatigue at time points beyond three months.

Future Directions

A natural next step that would add confidence to the findings regarding causal effects is to extend the current analysis to a third wave of panel data. Three-wave and multiwave panels have been extolled as ideal for causal analysis and have been noted for potential to estimate reciprocal effects (Finkel, 1995). Sample size becomes even more of a consideration for 3-wave models, however, as there are additional parameters to be estimated and attrition typically tends to grow over more extended periods.

Ideally, the current findings should be replicated in larger samples and with multiple validated scales for fatigue. A larger heterogeneous sample similar to that of the INCPAD study would allow the main analysis to be repeated with enough power to detect smaller effects, if they exist. More importantly, a much larger sample would allow the model to be tested by type and phase of cancer, which would lead to resolution of the unanswered question as to whether depression may have a causal influence on CRF in specific types or phases of cancer. A larger sample could also more readily be extended to multiple waves. It would also be informative to complete a similar study with a nonpharmacologic intervention for fatigue, and test for causal influences on depression.

The current study underscores the need for future research attention to be focused on understanding CRF. Given how highly prevalent and disabling it is, surprisingly little is currently known about its etiology or how to help those who suffer from it. The current findings add new information to this under-studied but important issue. It is hoped that this work will be replicated and extended in ways that will inform the development of effective treatments.

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APPENDICES

Appendix A

Reviews of Prevalence, Correlates, and Patterns of CRF

	Demo-graphic factors	Cancer type or site	Stage of cancer	Type of treatment	Bio markers	Depression & anxiety	Other Symptoms (e.g.sleep, pain, dyspnea)	Other key findings
Lawrence (2004) 93 studies	Mixed	Mixed	Mixed	Mixed	-	+	+	Occurrence rates ranged from 4% to 91%. Cancer patients' fatigue was higher than in comparison groups, both during and after treatment. CRF was also associated with psychosocial factors
Prue (2006) 44 studies	Mixed	+	-	-	+	+	+	CRF persists following cancer treatment; survivor fatigue more severe than in comparison groups with no cancer history. Level of physical activity strongly negatively associated with CRF
Servaes (2002) 54 studies	-	-	-	?		+	+	Prevalence of CRF ranged from 25% to 99%. In studies with comparison groups, fatigue in cancer patients was more frequent and severe than in groups with no cancer history

+ = Found to be correlated; - = Not correlated, ? = Inconclusive

Appendix B

Summary of Studies Examining Relationship of Cancer-Related Fatigue With Depression and Anxiety

Study	Cancer Sample & Control group	Treatment Status	Fatigue Measure	Depression Measure	Anxiety Measure	Fatigue-Depression *R or OR*	Fatigue-Anxiety *R or OR*	Key findings of study relevant to this review
Andrykowski (1998) Longitudinal	N = 88 BC pts. Control = 88 age-matched women without BC	Post-treatment; mean is 28 mos. Initial assessment & 4-mo followup.	Chalder Fatigue Scale; PFS	CES-D		0.68 $p < 0.01$		BC pts report more fatigue (but not depression) than controls. Fatigue may be chronic & unrelated to severity of treatment or time since completion.
Blesch (1991) Cross-sectional	N = 77 BC (44), or Lung cancer (33).	Receiving chemotherapy or RT.	VAS-fatigue	POMS-D	POMS-A	0.46 $p = 0.0001$	0.40 $p = .0005$	Fatigue correlated with pain but not with psychological or biochemical variables. Depression and anxiety correlated with one another..
Bower (2006) Longitudinal	N = 763 Long-term BC survivors	Assessment at 1-5, and 5-10 yrs after diagnosis	SF-36 vitality subscale	CES-D		OR = 1.17 $P < 0.0001$		Longitudinal predictors of fatigue included depression, cardiovascular problems, and type of treatment. 34% reported significant fatigue 5-10 yrs after diagnosis; 21% at both assessment points, indicating persistence
Bower (2000) Cross-sectional	N = 1,957 Disease-free BC survivors	1-to-5 yrs post-treatment	SF-36 energy/fatigue subscale	CES-D		OR = 1.13 $p = .0001$		The strongest predictor of fatigue was depression, followed by pain. Majority of participants did not experience more fatigue than general population, though a subgroup reported severe, persistent fatigue.
Bruera (1989) Cross-sectional	N = 64 Advanced BC	Receiving chemotherapy or hormonal therapy	Customized 4-test asthenia assessment	SCL-90 depression subscale	SCL-90 anxiety subscale	0.62 < 0.001	0.42 < 0.05	Asthenia correlated with depression & psychological distress, but not with nutritional status, lean body mass, tumor mass, anemia, or type of treatment.

Study	Cancer Sample & Control group	Treatment Status	Fatigue Measure	Depression Measure	Anxiety Measure	Fatigue-Depression *R or OR*	Fatigue-Anxiety *R or OR*	Key findings of study relevant to this review
Byar (2006) Longitudinal.	N = 25 Stage I or II BC	Chemotherapy post-surgery. Assessed at base-line, treatment 4, & 60-days and 1 yr after treatment.	PFS, Daily fatigue intensity item, SES fatigue items	HADS-D	HADS-A	NS- T1 0.618 -T2 p = 0.002 0.789 -T3 p < 0.001 0.510-T4 p = 0.031	NS- T1 NS- T2 0.620-T3 p = 0.004 0.480- T4 p = 0.044	Fatigue levels were moderately intense during treatments & decreased over time. Anxiety was highest at baseline, & depression was highest during the 4th chemotherapy treatment. Higher fatigue compromises QoL.
Chan (2005) Longitudinal	N = 27 Advanced lung cancer	Receiving palliative RT. Assessed at baseline & 2 times during RT.	VAS		VAS		0.36-Base ns 0.49 T2 p < 0.05 0.53 T3 p < 0.01	Prevalence of breathlessness, fatigue, & anxiety ranged from 59% to 96%, with intensity becoming worse at Time 2 and 3. This symptom cluster had high internal consistency across 3 time points.
Dimeo (2004) Cross-sectional	N = 71 Hematological malignancies without relapse	At least 3 mo after treatment	FACT-F	CES-D		0.84 p < 0.0001		Fatigue was related to depression & reduced performance status. No correlation between fatigue & impairment of thyroid function, anemia, or persistent activation of immune system.
Dimeo (1997) Cross-sectional	N = 78 Solid tumors or hematological malignancies		POMS-F	POMS-D SCL-90 Depression	SCL-90 Anxiety	0.61 POMS-D 0.68 SCL-90 p < 0.001	0.63 p < 0.001	Fatigue weakly associated with physical performance but strongly correlated with depression, somatization, & anxiety. Lower physical performance was associated with higher scores in psychological variables.
Fernandes (2006) Cross-sectional	N = 25 Female inpatients. Control N = 25 Healthy volunteers	Varied	EORTC QLQ-C30 fatigue subscale, BFS	HADS-D	HADS-A	0.63 p = 0.002	0.37 ns	Fatigue severity was correlated with low QoL, depression, constipation, & decreased physical function. Fatigue severity was not related to impairment in sleep & circadian rhythm.

Study	Cancer Sample & Control group	Treatment Status	Fatigue Measure	Depression Measure	Anxiety Measure	Fatigue-Depression *R or OR*	Fatigue-Anxiety *R or OR*	Key findings of study relevant to this review
Fillion (2003) Cross-sectional.	N = 604 BC Prostate cancer	RT or other therapy underway or recently completed	MFI-15	HADS-D	HADS-A	0.58 significant but no p-value	0.37 significant no p-value	This was validation study: the MFI-5 showed good psychometric qualities for assessment of CRF
Fleer (2005) Longitudinal	N = 52 Stage 1 or disseminated non-seminomatous testicular tumor	Within 1 mo. orchidectormy & 3 & 12 mo later	MFI-20		STAI		0.51 $p < 0.001$	Older age, trait anxiety & early fatigue predicts fatigue. 1 yr after orchidectomy. Trait anxiety had causal effect on all fatigue subscales. Fatigue is not enduring problem in testicular cancer, with treatment only having an impact on fatigue levels shortly after treatment.
Fossa (2003) Cross-sectional. Mail survey comparing 3 groups	N = 1038 survivors 791 testicular cancer &247 Hodgkin's disease Control N = 1112 general population	Testicular cancer survivors (TCS) treated at least 4 yrs earlier.	FQ	HADS-D	HADS-A	OR = 1.1.83 $P < 0.001$	OR = 1.190 $P < 0.001$	16% of long-term survivors of testicular cancer had chronic fatigue, with age, anxiety, depression, & comorbidity as predictors. The highest & lowest mean scores of anxiety & depression were in the youngest TCS. Anxiety is a larger problem among TCS than depression, especially among the youngest.
Fox (2006) Cross-sectional	N = 51 Lung cancer recruited via web	Varied; 94% had undergone some treatment pre-study	SF-36	SF-36		0.44 $p = 0.01$		Depression, fatigue, & pain found in majority of survivors, with pain being the least common. Fatigue was the most intense & correlated with depression.
Gaston-Johansson (2000) Cross-sectional analysis of RCT	N = 110 Stage II, III or IV BC	Scheduled for autologous bone marrow transplantation	VAS	BDI	STAI	0.32 $p < 0.01$	0.43 $p < 0.001$	Bundled intervention (education, cognitive restructuring, & relaxation with imagery) reduced fatigue & nausea. Both groups had mild depression after treatment. The treatment group experienced mild anxiety compared to moderate anxiety in controls.

Study	Cancer Sample & Control group	Treatment Status	Fatigue Measure	Depression Measure	Anxiety Measure	Fatigue-Depression *R or OR*	Fatigue-Anxiety *R or OR*	Key findings of study relevant to this review
Geinitz (2004) Longitudinal	N = 38 Localized BC after radiotherapy	Assessment at 8 days before RT & 2 mo and 2.5 yrs post-treatment	FAQ VAS for fatigue	HADS-D	HADS-A	0.56 & 0.62 $p < 0.001$	0.62 & 0.47 $p < 0.001$ & $p = 0.003$	Chronic fatigue correlated closely with psychological distress. Pretreatment fatigue, anxiety and depression were risks for chronic fatigue. Fatigue 2.5 yrs after RT did not increase above baseline levels
Geinitz (2001) Longitudinal	N = 41 BC	Post-operative RT after surgery. Assessed before, weekly during, & 2 mo. after end of RT	FAQ VAS, intensity	HADS-D	HADS-A	0.56 $p < 0.001$	0.67 $p < 0.001$	Fatigue increased during RT. Neither anxiety nor depression increased during RT. VAS correlated with HADS-D only for wks 2 & 5 (0.48 & 0.44) & .with HADS-A only for wks 2 & 5 (0.43 & 0.41)
Geiser (2007) Longitudinal	N = 54 Cancer pts with anemia Control N = 25 Non-anemic pts	Treatment group assessed before start of epoetin alfa treatment & at 4, 8, 12, & 26 wks	FACT-F	HADS-D	HADS-A	0.67 - 0.73 mean = 0.70 p not reported	Not reported	Depression & QoL before treatment correlated with reduction of fatigue during treatment. Anxiety did not correlate.
Glaus (1998) Cross-sectional	N = 77 Cancer pts. Controls 77 healthy hospital workers	Currently receiving treatment	FAQ	HADS-D	HADS-A	0.54 no p-value	0.48 no p-value	This is a scale development study. FAQ was found to be reliable & valid.

Study	Cancer Sample & Control group	Treatment Status	Fatigue Measure	Depression Measure	Anxiety Measure	Fatigue-Depression *R or OR*	Fatigue-Anxiety *R or OR*	Key findings of study relevant to this review
Haghighat (2003) Cross-sectional	N = 112 BC	During treatment or at follow-up exam	CFS	HADS-D	HADS-A	OR = 1.3 P = 0.003	OR = 1.2 P = 0.04	Prevalence of fatigue, anxiety, & depression was 49%, 16% & 32% respectively. Fatigue predicted by anxiety depression, pain, tamoxifen use, having mastectomy.
Hann (2000) Cross-sectional	N = 342 Cancer pts	Varied.	FSI	CES-D		0.55 p < 0.01		FSI was found to be a reliable & valid measure of fatigue in a heterogenous sample of cancer pts.
Hann (1999) Longitudinal	N = 31 BC Control N = 49 women with no cancer history	Undergoing Autologous Stem Cell Transplantation (ASCR).	POMS-F FSI	CES-D	STAI	0.77 p < 0.001	0.52 p < 0.01	BC pts reported worse depression than controls & pts' depression worsened over course of treatment. Pts' anxiety was not significantly higher than controls & did not change during ASCR. Worse fatigue during ASCR was associated with worse depression & anxiety.
Hann (1998) Longitudinal	N = 220 Disease-free BC pts	Varied	FSI	CES-D	STAI	0.46 p < 0.001	0.48 p < 0.001	FSI found to be a reliable & valid measure of fatigue. Women with BC had more fatigue during & after treatment than other women of similar age.
Hann (1997) Cross-sectional	N = 43 BC Control N = 43 women with no cancer history	Disease free, 3 mo. after bone marrow transplant (BMT).	POMS-F FSI	CES-D	STAI	0.80 p < 0.001	0.65 p < 0.001	Fatigue was more frequent & severe for BMT recipients & had greater impact on functioning & QoL. Fatigue was more severe for those in whom more time had passed since BMT.
Hwang (2003) Cross-sectional	N = 180 Male cancer pts	Varied	BFI FACT-F MSAS-SF lack-of-energy item	Zung SDS (dropped 3 somatic items)		-0.70 (BFI global) P < 0.0001 -0.68 FACT-F 0.61 MSAS		All three fatigue measures showed strong correlation with depression. The lack-of-energy single item yielded similar information as multi-item scales & may provide a simple way to assess fatigue.

Study	Cancer Sample & Control group	Treatment Status	Fatigue Measure	Depression Measure	Anxiety Measure	Fatigue-Depression *R or OR*	Fatigue-Anxiety *R or OR*	Key findings of study relevant to this review
Kim (2006) Longitudinal. Secondary analysis of trial	N = 525 Cancer patients	Chemotherapy underway	FSCL	CES-D	POMS-SF Anxiety Scale	0.67 T1 0.72 T2 0.73 T3 0.71 T4 p not reported		2 dimensions of psychological factors—arousal & valence—predicted changes in fatigue & depression. Fatigue changes depended more on valence; depression changes on both valence & arousal.
Kirsh (2001) Cross-sectional.	N = 52 Cancer pts in urban & rural centers	Varied.	Zung item, "I get tired for no reason." Also, FACT-An	Zung SDS		0.63 $p < 0.0001$ (Zung item)		The single fatigue item from the Zung SDS was highly correlated with the Zung SDS and the FACT-An. Use of the single Zung fatigue item as a brief measure for fatigue was supported.
Loge (2000) Cross-sectional	N = 421 Hodgkin's disease survivors	Varied.	FQ	HADS-D	HADS-A	0.49 $p < 0.001$	0.44 $p < 0.001$	26% of Hodgkin's disease survivors had substantial fatigue for ≥ 6 mo. These pts had higher anxiety & depression, but not more past psychiatric problems.
Meek (20000 Longitudinal	N = 212 Cancer patients	Pts receiving treatment for cure or local control. treatment	POMS-F MAF LFS MFI	POMS-D	POMS-T	0.53 POMS-F 0.53 MAF 0.41 LFS-F - 0.37 MFI $p < 0.05$	0.57 POMSF 0.52 MAF 0.47 LFS-F - 0.40 MFI $p < 0.05$	Results supported validity of three of four fatigue scales tested; MFI required further testing.
Mock (1997) Longitudinal	N = 46 Breast cancer pts	Post surgery & at start, midpoint and end of 6-wk RT	PFS	VAS	VAS	0.61 $p < 0.001$	0.60 $p < 0.001$	Exercise group had significant improvements in physical functioning & symptom intensity, particularly fatigue, anxiety, & sleep problems.
Morant (1996) Cross-sect.	N = 225 Cancer pts	Varied.	LASA	LASA		0.48 $p < 0.0001$		Fatigue correlated with mood, weakness, lack of concentration, lack of appetite, insomnia, & pain.

Study	Cancer Sample & Control group	Treatment Status	Fatigue Measure	Depression Measure	Anxiety Measure	Fatigue-Depression *R or OR*	Fatigue-Anxiety *R or OR*	Key findings of study relevant to this review
Morrow (2003) Longitudinal	N = 549 235 randomized to placebo condition	Receiving chemotherapy. Assessment at cycles 2, 3, & 4	FSCL MAF POMS-F	CES-D POMS-D		0.61 P < 0.01		Difference found between treatment and control groups in depression, but no difference was detected in fatigue.
Munch (2006) Cross-sectional	N = 130 Advanced cancer pts	Palliative care	MFI-20 Subscales Physical	HADS-D	HADS-A	0.52 p < 0.0001	0.23 p = 0.011	Fatigue levels were high. Depressed pts had higher levels on 4 fatigue subscales (general, mental, reduced activity, reduced motivation) but not on physical fatigue
Okuyama (2001) Cross-sectional	N = 157 Advanced lung cancer pts	No active cancer in preceding 4 wks	CFS FNS	HADS-D	HADS-A	OR = 1.24 p = 0.001		Half the sample had clinical fatigue. Dyspnea on walking, appetite loss, & depression were correlated.
Okuyama ((2000) Cross-sectional	N = 307 Cancer pts	Varied	CFS	HADS-D	HADS-A	0.69 p < 0.001	0.69 p < 0.001	Results suggest the CFS is a brief, valid, and feasible measure of CRF.
Okuyama (2000) Cross-sectional	N = 134 Disease-free BC	Post-surgery & not in active treatment	CFS	HADS-D		0.63 p < 0.001	0.52 p < 0.001	Depression, dyspnea, & insufficient sleep accounted for 46% of fatigue variance. Disease & treatment variables (e.g., disease stage, time since surgery) were not correlated with fatigue.
Passik (2002) Cross-sectional	N = 200 100 pts from urban, 100 from rural sites	Receiving chemotherapy	FACT-F	Zung-SDS (dropped 9 somatic items)		-0.66 p < 0.001		Depressed pts more likely to have heard about fatigue interventions, and wanted medications for fatigue Few urban-rural differences were noted.

Study	Cancer Sample & Control group	Treatment Status	Fatigue Measure	Depression Measure	Anxiety Measure	Fatigue-Depression *R or OR*	Fatigue-Anxiety *R or OR*	Key findings of study relevant to this review
Pirl (2008) Longitudinal	N = 52 Men with advanced or recurrent prostate cancer	Receiving hormone therapy. Assessed pretreatment, 6 mo & 12 mo	FSS	BDI		0.34 *T1 0.69** T2 0.58** T3 *p = 0.02 **p = 0.001		Fatigue increased significantly over the study period but depression do not change.
Prieto (2006) Longitudinal	N = 220 Hematologic cancer	Hospitalized for stem cell transplant. Assessment at admission, day of transplant, & 7- & 14-day post-surgery	Validated 1-item energy scale	HADS-D	HADS-A	-0.45** T1 -0.25** T2 -0.27** T3 -0.22* T4 * p < 0.01 ** p < 0.001	-0.26** T1 -0.20* T2 -0.21* T3 -0.16 T4 * p < 0.01 ** p< .001	Depression was variable most consistently & strongly associated with fatigue, measured using an energy level scale validated to capture the most physical dimension of fatigue. Baseline depression showed significance or a trend toward significance in predicting subsequent fatigue scores during hospitalization.
Redeker (2000) Cross-sectional	N = 263 Cancer pts	Undergoing chemotherapy	SDS	POMS-D	POMS-T	0.43 p < 0.001	0.44 p < 0.001	Symptoms & psychological variables explained 47% of variance in QoL, with the largest proportion explained by depression. Fatigue & insomnia explained only 4%
Respini (2003) Cross-sectional	N = 77 Cancer outpatients age 60 and older	During treatment with chemotherapy or pamidronate	FSI	GDS		0.29 p < 0.01		Fatigue was almost universal. Fatigue disruptiveness higher for women (p < 0.007). Depression was signify-cantly related to fatigue severity & disruptiveness.

Study	Cancer Sample & Control group	Treatment Status	Fatigue Measure	Depression Measure	Anxiety Measure	Fatigue-Depression *R or OR*	Fatigue-Anxiety *R or OR*	Key findings of study relevant to this review
Reuter (2006) Cross-sectional	N = 353 BC recently diagnosed	Post-surgery & within 12-mo. of diagnosis	POMS-F	HADS-D		0.59 P < 0.001		Fatigue was positively associated with depression & pain but inversely related to age. The association between coping & fatigue was weak.
Roscoe (2002) Longitudinal.	N = 78 BC pts	At 2nd & 4th on-study chemotherapy cycles. Assessment 7 days after each treatment. Circadian rhythm monitored over 72-h period.	MAF FSCL	CES-D HDI		FSCL, CES-D 0.63 FSCL&HDI 0.66 MAF,CES-D 0.66 MAF&HDI 0.68 (All p < 0.01)		Changes in the fatigue and depression measures from the 2nd treatment to the 4th correlated with changes in circadian rhythm. Suggests circadian rhythm disruption may contribute to fatigue & depression in cancer
Schneider (1998) Cross-sectional	N = 54 Cancer pts	Receiving RT or chemotherapy	MFI-20	BDI		0.56 p < 0.001		In this construct validation study, MFI-20 was found to be a potentially useful measure of fatigue.
Schumacher (2002) Longitudinal	N = 101 Pts newly diagnosed with acute myeloid leukemia	Undergoing treatment. Assessment at 12 sequential time points over 3 years.	EORTC QLQ-C30 fatigue subscale,	POMS-D		0.38** T2 0.38** T3 0.37* T4 0.34* T5 0.52** T7 0.47** T8 0.39* T9 n.s. T1,T6, T10,T11,T12 *p < 0.05 **p < 0.01		Depression was significantly inversely correlated with emotional functioning subscale of the QLQ-C30 throughout the study but its correlation with the fatigue subscale was nonsignificant at 5 of 12 time points.

Study	Cancer Sample & Control group	Treatment Status	Fatigue Measure	Depression Measure	Anxiety Measure	Fatigue-Depression *R or OR*	Fatigue-Anxiety *R or OR*	Key findings of study relevant to this review
Servaes (2007) Longitudinal.	N = 150 Disease-free BC survivors diagnosed before age 50.	≥ 6-mo post-treatment. and then monthly for 2 yrs	POMS-F	BDI-primary care	STAI	N/A	0.612 P < 0.001	Fatigue persisted in a quarter of disease-free cancer pts during 2-yr follow-up. High anxiety, impairment in role functioning, & low sense of control over fatigue at baseline predicted persistent fatigue.
Servaes (2000) Cross-sectional.	N = 85 Disease-free cancer pts Comparison N = 16 CFS pts	≥ 6-mo post-treatment	CIS	BDI	STAI	0.73 p not reported	0.60 p not reported	Severity of fatigue in cancer pts was comparable to that of pts with CFS. Severe fatigue is associated with problems of concentration and motivation, reduced physical activity, emotional health, and pain. Highest frequence of severe fatigue was in pts treated with RT.
Smets (1998A) Longitudinal. Same sample as Visser 1998	N = 250 Cancer pts receiving RT.	Assessment before RT, every 2 wks during treatment, & 2 wks post-RT..	MFI-20	CES-D		0.43 p < 0.001		Fatigue increased over the course of RT, followed by a decrease after RT ended, suggesting an acute radiation effect . Pre-treatment fatigue was greatest predictor of post-treatment fatigue; fatigue after RT only slightly but significantly higher than before RT
Smets (1998B) Cross-sectional	N = 154 Disease-free cancer patients after RT. Control N = 139 General population	9 mo after RT.	MFI-20	CES-D		0.49 p < 0.001		Fatigue in disease-free cancer pts did not differ from general population, although 39% listed fatigue as one of their 3 most distressing symptoms, & 34% reported fatigue following treatment was worse than expected. Overall QoL negatively related to fatigue (r = -0.46).
Smets (1996) Cross-sectional	N = 116 Cancer pts	During RT	MFI-20	HADS-D w/o item 8	HADS-A	0.77 p < 0.001	0.51 p < 0.001	Results support the validity of the MFI-20.

Study	Cancer Sample & Control group	Treatment Status	Fatigue Measure	Depression Measure	Anxiety Measure	Fatigue-Depression *R or OR*	Fatigue-Anxiety *R or OR*	Key findings of study relevant to this review
Stein (1998) Longitudinal.	N = 275 BC pts Control N = 70 Women with no cancer history	Received or under-going RT, BMT, or chemotherapy	MFSI	CES-D	STAI	0.68 $p < 0.05$	0.58 $p < 0.05$	The MFSI may be useful in identifying patterns of fatigue within individuals & across treatment modalities.
Stone (2001) Longitudinal.	N = 69 Pts with breast or prostate cancer	Assessment prior to starting RT & within 1 wk of completion	FSS BFS EORTC QLQ-C30	HADS-D w/o item 8	HADS-A	0.75 $p < 0.001$ (at baseline)	0.50 $p < 0.001$ (at baseline)	No increase in FSS scores, but modest significant increase in 3 other measures of fatigue. Combination of fatigue & anxiety at baseline predicted 54% of variation in fatigue at completion of RT. Depression had strongest association with fatigue severity.
Stone (2000) Cross-sectional.	N = 227 Prostate cancer, BC, non-small-cell lung cancer, or advanced cancer Control N = 98	Pts about to begin receiving treatment except for group with advanced cancer, who were 4 wks post-treatment	FSS EORTC QLQ-C30	HADS-D w/o item 8	HADS-A	0.67 $p < 0.001$	0.41 $p < 0.001$	Severe fatigue was present in 15%, 16%, 50%, & 78%, respectively, of pts recently diagnosed with BC, recently diagnosed with prostate cancer, inoperable non-small cell lung cancer, & palliative care inpatients. Psychological distress, dyspnea, pain & overall disease burden accounted for 56% of fatigue.
Stone (2000) Longitudinal	N = 62 Prostate cancer patients	Pts starting first-line hormone therapy. Assessment at start of hormone therapy and 3 mo later.	FSS EORTC-QLQ C30 BFS VAS	HADS-D w/o item 8	HADS-A	0.46 $P < 0.001$ FSS	0.52 $P < 0.001$	Mean FSS scores increased after 3 mo treatment. Anxiety/depression symptoms accounted for 28% of variance in fatigue at baseline. Increases in fatigue did not appear to be related to increases in psychological complaints.

Study	Cancer Sample & Control group	Treatment Status	Fatigue Measure	Depression Measure	Anxiety Measure	Fatigue-Depression *R or OR*	Fatigue-Anxiety *R or OR*	Key findings of study relevant to this review
Stone (1999) Cross-sectional	N = 95 Inpatients with advanced cancer Control N = 98 without cancer	No RT or chemotherapy in previous 4 wks.	FSS	HADS-D w/o item 8	HADS-A	0.16 ns	0.16 ns	75% of advanced cancer pts had severe subjective fatigue (fatigue greater than that of 95% of the control group). Fatigue severity associated with pain & dypsnoea; anxiety & depression were significant correlates only in controls.
Sugawara (2005) Cross-sectional	N = 79 BC pts w/o major depression & disease free 3 yrs post surgery	Disease-free status & receiving no therapy other than tamoxifen	CFS	POMS-D	STAI	0.36 $p < 0.01$	0.36 $p < 0.01$	36.7% of disease-free BC pts without major depression exhibited fatigue, which was strongly associated with neuroticism. Depressive symptoms & anxiety were also significantly associated.
Tchekmediyian (2003) Longitudinal	N = 250 Lung cancer pts with anemiar	On chemotherapy. Assessment at baseline & after 4 wk of treatment.	FACT-F	BSI-Depression	BSI-Anxiety	-0.44 $p < 0.001$	-0.45 $p < 0.001$	Improvements in fatigue were associated with reductions in anxiety & depression. In a multiple regression model of change in anxiety & depression, change in fatigue was the only significant variable
Tsai (2007) Cross-sectional.	N = 77 Terminally ill cancer	Institutional hospice	POMS-F	HADS-D	HADS-A	0.73 $p < 0.0001$	0.54 $p < 0.0001$	Terminally ill pts had moderate to severe levels of fatigue. Fatigue was associated with overall symptom distress, depression, anxiety, & performance status.
Visser (1998) Longitudinal	N = 250 Cancer pts scheduled for RT	In RT. Assessment 2 wks pre-treatment, 2 wks post treatment, 9 mo later.	MFI-20	CES-D (mood only)		0.35 T1 0.43 T2 0.48 T3 $p < 0.001$		Just after RT, fatigue increased or remained stable, while depression decreased. 9 mo later, fatigue had decreased while depression was stable. No strong causal relationship was found between depression & fatigue.

Study	Cancer Sample & Control group	Treatment Status	Fatigue Measure	Depression Measure	Anxiety Measure	Fatigue-Depression *R or OR*	Fatigue-Anxiety *R or OR*	Key findings of study relevant to this review
Wu (2006) Cross-sectional	N = 172 BC pts	Undergoing chemotherapy	WCFS	GDS		0.60 p not reported		In this scale development study, the revised WCFS was found to be reliable & valid.
Young (2006) Cross-sectional.	N = 69 Disease-free BC pts	At least 6 mo post-treatment	MFSI FSI Structured interview	HADS-D	HADS-A	0.78, 0.79 $p < 0.01$	0.70, 0.75 $p < 0.01$	19% met draft ICD-10 criteria for cancer-related fatigue. Psychological distress & beliefs about activity predicted fatigue directly.

BDI	Beck Depression Scale
BFI	Brief Fatigue Inventory
BFS	Bi-dimensional Fatigue Scale
BSI	Brief Symptom Inventory
CFS	Cancer Fatigue Scale
CES-D	Center for Epidemiological Studies Depression Scale
CIS	Checklist Individual Strength
EORTC	European Organization for Research & Treatment of Cancer 30-Item
FACT-F	Functional Assessment of Cancer Therapy- Fatigue Subscale
FAQ	Fatigue Assessment Questionnaire
FNS	Fatigue Numerical Scale
FQ	Fatigue Questionnaire
FSCL	Fatigue Symptom Checklist, 30-item
FSI	Fatigue Symptom Inventory
FSS	Fatigue Symptom Severity
GDS	Geriatric Depression Scale
HADS-A	Hospital Anxiety & Depression Scale – Anxiety
HADS-D	Hospital Anxiety & Depression Scale – Depression
HDI	Hamilton Depression Inventory
LASA	Linear Analogue Self-Assessment
LFS-F	Lee Fatigue Scale-Fatigue subscale
MAF	Multidimensional Assessment of Fatigue
MSAS-SF	Memorial Symptom Assessment Scale Short Form
MFI-20	Multidimensional Fatigue Inventory
MFI-15	Mulitdimensional Fatigue Inventory – Short form
MFSI	Multidimensional Fatigue Symptom Inventory
PFS	Piper Fatigue Scale
POMS-D	Profile of Mood States depression-dejection subscale
POMS-F	Profile of Mood States fatigue-inertia scale
POMS-T	Profile of Mood States-tension/anxiety scale
SCL-90	Symptoms Checklist – 90
SDS	Symptom Distress Scale
SF-36	Short-Form 36 Health Status Survey
SES	Symptom Experience Scale
STAI	Spielberger Trait Anxiety Inventory
VAS	Visual Analog Scale, 100-meter
WCFS	Wu Cancer Fatigue Scale
Zung SDS	Zung Self-Rating Depression Scale

General fatigue scores are used for correlations when multiple fatigue types are reported

BC =	BC
CFS =	Chronic Fatigue Syndrome
N/A =	Not Available
RCT =	Randomized controlled trial
RT=	Radiotherapy
QoL=	Quality of life
BMT =	Bone marrow transplantation
Pt(s) =	Pt(s)

(Andrykowski, Curren, & Lightner, 1998; Blesch et al., 1991; Bower et al., 2006; Bower et al., 2000; Bruera et al., 1989; Byar, Berger, Bakken, & Cetak, 2006; Chan et al., 2005; Dimeo et al., 2004; Dimeo et al., 1997; Fernandes, Stone, Andrews, Morgan, & Sharma, 2006; Fillion, Gelinas, Simard, Savard, & Gagnon, 2003; Fleer, Sleijfer, Hoekstra, Tuinman, & Hoekstra-Weebers, 2005; Fossa, Dahl, & Loge, 2003; Fox & Lyon, 2006; Gaston-Johansson et al., 2000; Geinitz et al., 2001; Geinitz et al., 2004; Geiser et al., 2007; Glaus, 1998; Haghighat, Akbari, Holakouei, Rahimi, & Montazeri, 2003; Hann et al., 2000; Hann et al., 1999; Hann et al., 1998; Hann et al., 1997; Hwang, Chang, Rue, & Kasimis, 2003; Kim, Hickok, & Morrow, 2006; Kirsh, Passik, Holtsclaw, Donaghy, & Theobald, 2001; Loge, Abrahamsen, Ekeberg, & Kaasa, 2000; Meek et al., 2000; Mock et al., 1997; Morant, 1996; Morrow et al., 2003; Munch et al., 2006; Okuyama, Akechi, Kugaya, Hitoshi et al., 2000; Okuyama, Akechi, Kugaya, Okamura et al., 2000; Okuyama et al., 2001; Passik et al., 2002; Pirl, 2008; Prieto et al., 2006; Redeker, Lev, & Ruggiero, 2000; Respini et al., 2003; Reuter et al., 2006; Roscoe et al., 2002; Schneider, 1998; Schumacher et al., 2002; Servaes, Gielisson, Verhagen, & Bleijenberg, 2007; Servaes et al., 2000; Smets et al., 1996; Smets, Visser, Willems-Groot, Garssen, Oldenburger et al., 1998; Smets, Visser, Willems-Groot, Garssen, Schuster-Uitterhoeve et al., 1998; Stein, Martin, Hann, & Jacobsen, 1998; Stone et al., 1999; Stone, Hardy et al., 2000; Stone, Richards, A'Hern, & Hardy, 2000; Stone et al., 2001; Sugawara et al., 2005; Tchekmedyian et al., 2003; Tsai et al., 2007; Visser & Smets, 1998; Wu, Wurwich, & McSweeney, 2006; Young & White, 2006)

Appendix C

Bivariate Correlations of Latent Variable Indicators Across Both Time-Points

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. sfenerT1	♦	.41	.48	.49	-.36	-.47	-.37	.41	.39	.33	.32	-.31	-.32	-.33
2. sflifeT1		♦	.29	.35	-.39	-.46	-.53	.29	.41	.30	.25	-.25	-.26	-.30
3. sfwornT1			♦	.74	-.34	-.46	-.33	.39	.26	.44	.38	-.31	-.30	-.27
4. sftireT1				♦	-.40	-.51	-.40	.36	.30	.43	.43	-.34	-.28	-.30
5. PHQ9T1					♦	.74	.65	-.27	-.34	-.36	-.24	.44	.43	.44
6. SCL20T1						♦	.74	-.35	-.42	-.41	-.31	.53	.58	.53
7. MHI3T1							♦	-.27	-.43	-.33	-.25	.46	.43	.56
8. sfenerT2								♦	.53	.53	.56	-.48	-.51	-.44
9. sflifteT2									♦	.49	.45	-.54	-.59	-.63
10.sfwornT2										♦	.78	-.60	-.58	-.51
11. sftireT2											♦	-.54	-.50	-.46
12. PHQ9T2												♦	.85	.73
13. SCL20T2													♦	.76
14. MHI3T2														♦

Note. Fatigue indicators are sfener, sflife, sfworn, sftire. Depression indicators are PHQ9, SCL20, MHI3. T1 = baseline; T2 = 3 months. Negative correlations suggest a positive association between fatigue and depression because higher vitality scores suggest less fatigue whereas higher depression scores suggest worse symptoms. All correlations are significant at the 0.01 level (2-tailed

VITA

VITA

Linda F. Brown

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2007 - 2010	Predoctoral Fellowship: Training in Research for Behavioral Oncology and Cancer Control Program, Indiana University School of Nursing Funded by an R-25 CA 117865 training grant through the National Cancer Institute. PI: Victoria Champion.
2007	Article of the Year Award, *Journal of Psychiatric Nursing*

PUBLICATIONS

Brown, L.F., Kroenke, K., Theobald, D., &Wu, J. (in press). Comparison of vitality scale and Fatigue Symptoms Inventory in assessing cancer-related fatigue. *Supportive Care in Cancer.*

Bigatti, S.M, **Brown, L.F.,** Steiner, J., Miller, K.D. (2011). Breast cancer in a wife: How husbands cope and how well it works. *Cancer Nursing*, *34,* 3.

Brown, L.F., Kroenke, K., Theobald, D., Wu, J., and Tu, W. (2010). The association of depression and anxiety with health-related quality of life in cancer patients with depression and/or pain. *Psycho-Oncology, 19,* 734-741.

Brown, L.F., Davis, L.W., LaRocco, V A., & Strasburger, A. (2010). Participant perspectives on mindfulness meditation training for anxiety in schizophrenia. *American Journal of Psychiatric Rehabilitation.*

Brown, L.F. & Kroenke, K. (2009). Cancer-related fatigue and its associations with depression and anxiety: A systematic review. *Psychosomatics, 50,* 440-447.

Davis, L.W., Strasburger, A.M., & **Brown, L.F.** (2007). Mindfulness: An intervention for anxiety symptoms in schizophrenia. *Journal of Psychiatric Nursing*, *45*, 23-29

Brown, L.F. (2004). Psychology in a new light: Darwin's influence in the century after *The Origin of Species*. *The Journal of Graduate Liberal Studies*, IX: 2, 23-47.

PAPER AND SYMPOSIA PRESENTATIONS

Brown, L.F. (2010, November). Mindfulness-based stress reduction for persistent cancer-related fatigue: A pilot study. Symposium presentation at the Association for Behavioral and Cognitive Therapies annual convention, San Francisco, CA.

Brown, L.F. (2010, October). Depression and cancer-related fatigue: A cross-lagged panel analysis of causal effects. Podium presentation at The 2nd International Cancer Fatigue Symposium, Montreal, Quebec.

POSTER PRESENTATIONS

Brown, L.F., Kroenke, K., Rand, K.L., Bigatti, S.M. (2010, October). *Depression and cancer-related fatigue: A cross-lagged panel analysis of causal effects. Po*ster presented at The 2nd International Cancer Fatigue Symposium, Montreal, Quebec.

Johns, S., **Brown, L.F.,** Kroenke, K., Monahan, P., & Beck-Coon, K. (2010, May). *An acceptance-based model for treatment of cancer-related fatigue.* Poster presented at Indiana University Simon Cancer Center Cancer Research Day, Indianapolis, IN.

Brown, L.F., Kroenke, K. &, Wu, J. (2010, February). *Comparison of vitality scale and FSI in assessing cancer-related fatigue*. Poster presented at American Psychosocial Oncology Society national conference, New Orleans, LA.

Brown, L.F., Kroenke, K., Theobald, D., Wu, J., and Tu, W. (2009, May). *The association of depression and anxiety with health-related quality of life in cancer patients*. Poster presented at Indiana University Simon Cancer Center Cancer Research Day, Indianapolis, IN.

Brown, L.F. & Bigatti, S.M. (2008, March). *Differential relations of fatigue with psychological variables in patients with breast cancer and their spouses*. Poster presented at the annual meeting of the Society of Behavioral Medicine, San Diego, CA.

Davis, L.W. & **Brown, L.F.** (2008, April). *Mindfulness targeting anxiety symptoms of persons with schizophrenia: Results of a pilot study.* Poster presented at the 6th Annual Conference for Clinicians, Researchers, and Educators: Integrating Mindfulness-Based Interventions into Medicine, Health Care, and the Larger Society, Worcester, MA.

Brown, L.F. (2007, November). *Interest in mindfulness meditation training among older adults.* Poster session presented at a national conference on contemplative practices, Meditation and Spirituality: Scientific, Conceptual, and Applied Perspectives, Indiana State University, Terre Haute, IN.

TEACHING EXPERIENCE

March-April 2011	Instructor, Mindfulness-Based Stress Reduction, 8-week mindfulness meditation class for mental health practitioners. Division of Psychiatry, Geisinger Medical Center, Danville, PA
Spring 2010	Instructor, B365, Stress and Health, Department of Psychology, IUPUI
Fall & Spring 2007-2008	Teaching Assistant, Introduction to Counseling classes Department of Psychology, IUPUI.
Fall & Spring 2005-2006	Teaching Assistant, Psychology of Stress, Sports Psychology. Department of Psychology, IUPUI.

RESEARCH EXPERIENCE

1/2008 to present	Pilot Study of Mindfulness-Based Stress Reduction for Patients with Persistent Cancer-Related Fatigue Principle Investigator: Kurt Kroenke, M.D. Study Team: Shelley Johns, Linda F. Brown, Patrick Monahan, Kathleen Beck-Coon
1/2008 to 2010	Depression and Cancer-Related Fatigue: A Cross-Lagged Panel Analysis of Causal Effects Primary Mentor: Kurt Kroenke, M.D. Secondary Mentor: Silvia M. Bigatti, PhD
7/2006 to 8/2007	Mental Health Treatment Study Supervisors: Mike McKasson, LCSW; Roline Milfort, PhD
1/2007 to 3/2008	Mindfulness as an Intervention for Anxiety Symptoms in Schizophrenia Supervisor: Louanne Davis, PsyD
3/2006 to 7/2007	Interest in Mindfulness Meditation Among Older Adults Mentor, Principal Investigator: Silvia M. Bigatti, PhD

OTHER WORK EXPERIENCE

8/2005 to 5/2006	Graduate Assistant, Kelly School of Business, IUPUI Supervisors: Alexander Fedorikhin, PhD; Susan Mantel, PhD

Prior to Graduate School Admission

2000 to 2005	Vice President of Human Resources, RiverValley Behavioral Health (Community Mental Health Center) Owensboro, KY

TRAINING IN SPECIAL INTEREST AREAS

2009-2010	Teaching Apprenticeship in Mindfulness-Based Stress Reduction Mentor, Kathleen Beck-Coon, MD 28 hours of training and teaching experience over 10 weeks Indiana University School of Nursing
2009	Practicum in Mindfulness-Based Stress Reduction: Living Inside Participant-Practitioner Perspectives. Melissa Blacker, MA & Florence Meleo-Meyer, MS, MA 9-day, 66-hour practicum Center for Mindfulness, University of Massachusetts Medical School, Worcester, MA
2008	Mindfulness-Based Stress Reduction in Mind-Body Medicine: A 7-Day Professional Training. Jon Kabat-Zinn, PhD & Saki Santorelli, EdD Center for Mindfulness, Rhinebeck, NY
2008	Structural Equation Modeling with LISREL for Windows Gregory Hancock, PhD & Ralph O. Mueller, PhD 3-Day Workshop Chicago, IL
2007	Acquiring Skills to Implement Acceptance and Commitment Therapy Steven Hayes, PhD, 2-day workshop Philadelphia, PA
2007	Motivational Interviewing Workshop John Wryobeck, PhD, 3-day workshop Indianapolis, IN

PROFESSIONAL MEMBERSHIPS

Association for Behavioral and Cognitive Therapies
Association for Contextual Behavioral Science
American Psychological Association, student affiliate
American Psychology Association of Graduate Students
Indiana Psychological Association