Distinguishing Fatigue and Depression in Patients With Cancer

Paul B. Jacobsen, Kristine A. Donovan, and Michael A. Weitzner

In seeking to learn more about the etiology and treatment of fatigue in patients with cancer, clinicians and researchers have been challenged to understand how fatigue can be distinguished from depression. Approaches currently used to study fatigue and depression in patients with cancer appear to be of limited usefulness in distinguishing these phenomena. This conclusion is supported by a review of studies in which the single-symptom and symptom-cluster approaches were used to measure fatigue and depression concurrently in patients with cancer. The review yielded consistent evidence of high positive correlations between fatigue and depression, even when attempts were made to eliminate overlapping item content. A consideration of causal mechanisms suggests why it remains difficult to distinguish between fatigue and depression. In addition to fatigue being a possible cause of depression and depression being a possible cause of fatigue, both fatigue and depression can share a common cause. That is, certain forms of cancer and cancer treatment can cause both fatigue and depression. These different mechanisms have implications for efforts to distinguish fatigue and depression and to identify appropriate treatments. For example, recently developed diagnostic criteria for a clinical syndrome of cancer-related fatigue might be useful in identifying fatigue that is caused by a major depressive disorder for which antidepressant therapy is generally indicated. © 2003 Elsevier Inc. All rights reserved.

There is a growing recognition among oncology professionals that fatigue is one of the most common and distressing symptoms experienced by cancer patients. In seeking to learn more about the etiology and treatment of fatigue, clinicians and researchers alike have been challenged to understand how fatigue might be related to depression in patients with cancer. The need to understand this relationship stems from 2 basic facts: (1) fatigue, in addition to being a symptom of cancer and its treatment, is a symptom of certain mood disorders; and (2) depression, like fatigue, is relatively common among patients with cancer. To clarify the relationship of fatigue to depression in patients with cancer, we have identified 4 questions that are of particular importance and serve to organize this article. First, what are the conceptual similarities and differences between fatigue and depression? Second, to what extent does depression co-occur with fatigue, and how might they be distinguished? Third, what is the possible causal relationship between fatigue and depression? Fourth, what are the treatment implications of the relationship of fatigue to depression?

Any attempt to answer these questions should be based on empiric findings, and whenever possible, we have done so. However, given the limited amount of research on fatigue in patients with cancer, there is relatively little empiric evidence to answer several of our questions. We hope that, by identifying areas in which evidence is lacking, this article will stimulate additional and much-needed research into the relationship of fatigue to depression in patients with cancer.

What Are the Similarities and Differences Between Fatigue and Depression?

To understand the conceptual similarities and differences between fatigue and depression, it is necessary to consider how these concepts have been operationally defined. Our approach to this issue focuses on the different ways in which fatigue and depression have been assessed in patients with cancer. Three distinct approaches to the assessment of depression can be identified: the single-symptom approach, the symptom-cluster approach, and the clinical syndrome approach.

The single symptom approach refers to assessment methods that focus specifically on measuring depressed mood. This symptom can be measured as a continuous variable (for example, visual analog scales measuring severity of depressed mood) or a categorical variable (for ex-

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ample, clinical interview items measuring presence/absence of depressed mood).

The symptom-cluster approach refers to assessment methods that focus on measuring multiple symptoms of depression. A common approach to measuring depressive symptomatology in patients with cancer has been to administer a multi-item self-report scale such as the Beck Depression Inventory (BDI) or the Center for Epidemiologic Studies Depression Scale (CES-D). Both instruments assess a constellation of symptoms (depressed mood, loss of appetite, and difficulty concentrating) that are theorized to reflect the construct of depression. Because fatigue is generally regarded as one of the core symptoms of a depressive disorder, it is not surprising to find that many depressive symptomatology measures include at least one item assessing fatigue-related phenomena. For example, the BDI asks respondents to choose among alternatives ranging from “I don’t get any more tired than usual” to “I am too tired to do anything.” Similarly, on the CES-D, respondents are asked to rate the extent to which they “could not get going” from rarely or none of the time to most or all of the time.

The clinical syndrome approach refers to assessment methods that focus on detecting the presence of a mood disorder, such as major depressive disorder. As defined in the 4th edition of the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), a diagnosis of major depressive disorder requires the presence of 4 or more depressive symptoms during the same 2-week period in addition to depressed mood or loss of interest or pleasure in usual activities. Among the other symptoms whose presence counts toward the criterion of 4 or more symptoms is fatigue or loss of energy.

Fatigue can also be assessed as a single symptom, a cluster of symptoms, or a clinical syndrome. The single-symptom approach refers to assessment methods in which fatigue is conceptualized as a unidimensional phenomenon. Measures of fatigue severity such as the Profile of Mood States Fatigue Scale (POMS-F) exemplify this approach. Overlap can be identified between the single-symptom approach to measuring fatigue and both the symptom-cluster and clinical syndrome approaches to measuring depression.

The symptom-cluster approach refers to assessment methods in which fatigue has been conceptualized as a multidimensional phenomenon. Although the specific dimensions that characterize fatigue in patients with cancer remain a topic of debate, at least 2 teams of investigators have identified similar clusters of symptoms, including general symptoms (for example, tiredness), physical symptoms (for example, feelings of weakness or heaviness), and mental symptoms (for example, difficulty concentrating). Self-report measures reflecting this conceptualization of fatigue include the Multidimensional Fatigue Inventory (MFI) and the Multidimensional Fatigue Symptom Inventory (MFSI). Overlap can be identified between this approach to measuring fatigue and both the symptom-cluster and clinical syndrome approaches to measuring depression. For example, both multidimensional fatigue measures referred to here assess a general symptom of fatigue (such as tiredness) and a mental symptom of fatigue (such as difficulty concentrating) that are also included in instruments used to measure depressive symptomatology and to diagnose major depressive disorder.

The clinical syndrome approach represents a relatively new method of assessing fatigue in patients with cancer. Recognizing the need for a standard case definition, a group of investigators has proposed a set of criteria for the diagnosis of cancer-related fatigue (see Table 1). Examination of the criteria indicates that overlap exists between this approach to measuring fatigue and both the symptom-cluster and clinical syndrome approaches to measuring depression. As shown in Table 1, a diagnosis of cancer-related fatigue requires the presence of 6 or more symptoms listed under criterion A. Several of the symptoms listed (fatigue, sleep disturbance, diminished concentration, and decreased interest in usual activities) are also present in measures of depressive symptomatology and included in the diagnostic criteria for major depressive disorder.

Although similarities are present in approaches to measuring fatigue and depression, important differences can also be identified. Conceptualizations of fatigue include a number of symptoms that are not consistent with symptom-cluster and clinical syndrome conceptualizations of depression. These include generalized feelings of weakness or heaviness, postexertional malaise, and difficulty completing daily tasks as a result of fatigue. Moreover, clinical syndrome approaches to measuring fatigue and depression include criteria that seek to differentiate cancer-related fatigue from mood disorders. For example, crite-
Table 1. Proposed Criteria for Cancer-Related Fatigue

A. Six (or more) of the following symptoms have been present every day or nearly every day during the same 2-week period in the past month and at least one of the symptoms is significant fatigue.
- Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level
- Complaints of generalized weakness or limb heaviness
- Diminished concentration or attention
- Decreased motivation or interest to engage in usual activities
- Insomnia or hypersomnia
- Experience of sleep as unrefreshing or nonrestorative
- Perceived need to struggle to overcome inactivity
- Marked emotional reactivity (for example, sadness, frustration, or irritability) to feeling fatigued
- Difficulty completing daily tasks attributed to feeling fatigued
- Perceived problems with short-term memory
- Postexertional malaise lasting several hours

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
C. There is evidence from the history, physical examination, or laboratory findings that the symptoms are a consequence of cancer or cancer therapy
D. The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder, or delirium


rion D for cancer-related fatigue (in Table 1) states that this syndrome is not diagnosed if symptoms of fatigue are considered to be the primary consequence of a comorbid psychiatric disorder. Similarly, the DSM-IV criteria3 specify that major depressive disorder is not diagnosed if the symptoms present, including fatigue, are considered to be the direct physiological effects of substance use or a general medical condition such as cancer.

In summary, a review of measurement approaches indicates that overlap is present among all 3 approaches to measuring fatigue and both the symptom-cluster and clinical syndrome approaches to measuring depression. Based on these considerations, one would expect empirical studies to show that depression frequently co-occurs with fatigue in patients with cancer.

To What Extent Does Depression Co-Occur With Fatigue and How Might They Be Distinguished?

One way to determine the extent to which depression co-occurs with fatigue in patients with cancer is to examine the magnitude of correlations between measures of fatigue and depression administered concurrently to patients. Toward this end, a MEDLINE and PsycINFO search was conducted using the keywords fatigue and cancer. This search identified 30 studies that reported correlations between measures of fatigue and depression.

As shown in Table 2, depression was usually assessed in these studies using measures of depressive symptomatology, such as the CES-D, the BDI, or the depression subscale of the Hospital Anxiety and Depression Scale (HADS).9,9,11,38 Exceptions include 5 studies12,13,21,27,30 that used the POMS Depression Scale, a measure that reflects primarily depressed mood, and one study38 that included only mood items from the CES-D. No studies were identified that assessed mood disorders and fatigue concurrently in patients with cancer. Fatigue was usually assessed in these studies using measures of general fatigue severity such as the POMS Fatigue Scale or the MFI General Scale. Five studies were identified9,9,18,21,29 in which measures of general, mental, and physical symptoms of fatigue were administered to the same patients as part of a multidimensional approach.

Correlations between measures of fatigue and depression reported in the studies listed in Table 2 were positive and ranged from a low of .16 to a high of .80. The average correlation between fatigue and depression across studies was .54. Thus, on average, measures of fatigue and depression administered concurrently to patients with cancer shared approximately 29% of their variance. There was little evidence that the individual dimensions of fatigue were differentially related to depression. Specifically, in those studies that used a multidimensional approach,9,9,18,21,29 the average correlations among depression and gen-
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Table 2. Studies Assessing Fatigue and Depression Concurrently in Patients With Cancer (Cont’d)

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</tbody>
</table>

Abbreviations: r, Pearson or Spearman correlation coefficient; AML, acute myeloid leukemia; BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; CFS, Cancer Fatigue Scale; CHCS, Chalder Fatigue Scale; CIS, Checklist Individual Strength; EORTC, European Organization for Research and Treatment QLQ-C 30; FQ, Fatigue Questionnaire; FSCL, Fatigue-Symptom Checklist; FSI, Fatigue Symptom Inventory; FSS, Fatigue Severity Scale; HADS-D, Hospital Anxiety and Depression Scale—Depression Subscale; HFI, Hamilton Depression Inventory; LFS, Lee Fatigue Scale; MAF, Multidimensional Assessment of Fatigue; MFSI, Multidimensional Fatigue Inventory; PFSI, Multidimensional Fatigue Symptom Inventory; PFS, Piper Fatigue Scale; POMS, Profile of Mood States; RFS, Rhoten Fatigue Scale; SCL-90, Symptom Checklist 90; SDS, Symptom Distress Scale; VAS, Visual Analog Scale; ZSDS, Zung Self-Rating Depression Scale.

Overall, fatigue (.59), mental fatigue (.53), and physical fatigue (.57) were quite similar.

In the 6 studies using measures of depression that focused specifically on depressed mood, there was no evidence to suggest that limiting the assessment of depression to its mood component substantially diminished correlations with fatigue. Correlations between depression and fatigue in these studies averaged .43.

One of the studies listed in Table 2 included analyses designed specifically to examine the effects of overlap on correlations between measures of fatigue and depression. In this study, the MFI and the depression subscale of the HADS were administered concurrently to patients with cancer undergoing radiotherapy. The latter measure includes one item ("I feel as if I am slowed down") that would appear to overlap with fatigue. Correlations were computed between the MFI and both the original version of the HADS depression subscale and a version that excluded this item. Although correlations between depression and fatigue declined in size after exclusion of the item, the magnitude of the change was relatively modest. The average correlation between MFSI subscales and the HADS depression subscale was .68 before exclusion of the item and .60 after exclusion of the item. A similarly modest decline was evident in another study<sup>55</sup> in which correlations were reported between the Fatigue Severity Scale and the HADS depression subscale before and after exclusion of the same item.

In summary, empiric studies yield consistent evidence of a relatively high degree of correspondence between levels of fatigue and depression among patients with cancer. There is evidence to suggest, however, that the degree of correspondence is not solely a function of overlap in assessment approaches. First, correlations between fatigue and depression remained relatively high even when items reflecting phenomena associated with fatigue were removed from measures of depressive symptomatology.<sup>6</sup> Second, relatively high correlations have been observed between measures of fatigue and measures focusing specifically on depressed mood.<sup>12,13,21,27,30,38</sup>

Taken together, findings from these empiric studies suggest that the 2 fatigue-measurement approaches currently in use (the single-symptom approach and the symptom-cluster approach) are
of limited usefulness in attempts to distinguish fatigue from depression. One measurement strategy that has yet to be systematically investigated for its ability to distinguish these constructs is the clinical syndrome approach. With the advent of criteria for diagnosing a clinical syndrome of cancer-related fatigue, there is a need for research in which syndrome measures of fatigue and depression are administered concurrently to patients with cancer. To date, only one study of this type appears to have been published. This study is not listed in Table 2 because results are reported in terms of group comparisons rather than as a correlation coefficient. Participants in this study were 51 patients who had completed allogeneic or autologous bone marrow transplantation approximately 6 months previously. Results indicated that patients who met the diagnostic criteria for cancer-related fatigue had significantly higher levels of depressive symptomatology (as measured by the CES-D) than patients who did not meet the diagnostic criteria for cancer-related fatigue ($P = 0.02$).

**What Are the Causal Relationships Between Fatigue and Depression?**

As noted earlier, there is considerable evidence that levels of fatigue and depression correspond in some patients with cancer. At least 3 different causal relationships can be theorized to explain this correspondence. One possibility is that the fatigue produced by cancer and its treatment could result in patients becoming depressed. A second possibility is that fatigue could develop in patients with cancer as a consequence of their being depressed. A third possibility is that no causal relationship exists; instead, the correspondence could reflect the presence of a third factor that is the cause of both fatigue and depression in patients with cancer. As will be shown, there is evidence to suggest the existence of each of these mechanisms.

Two lines of research provide support for the view that patients with cancer can become depressed as a consequence of experiencing disease-related or treatment-related fatigue. One line of research consists of reports indicating that patients perceive disease-related or treatment-related fatigue as having adverse effects on their mood. For example, women undergoing transplantation for breast cancer reported more severe fatigue and greater interference of fatigue with their mood than a comparison group of women with no history of cancer. Differences between groups on these measures were evident only after the patients with breast cancer had started treatment. A second line of evidence consists of research examining whether, over the course of cancer treatment, fatigue predicts subsequent depression better than depression predicts subsequent fatigue. Of particular relevance is a study in which fatigue and depression were assessed before the start of radiotherapy treatment and 2 weeks after treatment completion. Pretreatment fatigue severity accounted for 11% of the variability in subsequent depressed mood, whereas pretreatment depressed mood accounted for only 4% of the variability in subsequent fatigue severity. Additional supportive evidence comes from a study that examined relations between psychiatric disorder (mood, anxiety, and adjustment disorders) and fatigue in women previously treated with adjuvant chemotherapy for breast cancer. The presence of a psychiatric disorder before cancer diagnosis was not related to fatigue severity after chemotherapy treatment; in contrast, more severe fatigue after chemotherapy treatment was related to the concurrent presence of a psychiatric disorder.

The possibility that patients with cancer can develop fatigue as a consequence of being depressed is intuitively obvious. Actually demonstrating this relationship represents a methodologic challenge because most patients with cancer can also develop fatigue as a consequence of their disease or its treatment. There is, however, indirect evidence to support the possibility that fatigue in patients with cancer can occur as a consequence of depression. Research has shown that patients with a prior history of depression are more likely to develop mood disorders after the diagnosis of cancer. Evidence indicating that these patients also experience worse fatigue than patients without mood disorders would be consistent with the possibility that fatigue can occur as a consequence of depression. Another indirect piece of evidence consists of reports indicating that reliance on specific forms of coping characteristic of depressed individuals is related to fatigue severity in patients with cancer. For example, among women with breast cancer previously treated with chemotherapy, greater reliance on catastrophizing (a coping strategy char-
acterized by negative self-statements and overly negative thoughts about the future) was associated with more severe fatigue.\textsuperscript{90} Greater reliance on this coping strategy also has been related to higher levels of depressive symptomatology in patients with breast cancer.\textsuperscript{52}

There is considerable evidence suggesting that the correspondence between fatigue and depression in patients with cancer might be the result of a third causal factor. Along these lines, attention has focused on certain cancers that are believed to cause depressive symptoms. Pancreatic cancer is one neoplasm that appears to display these characteristics. The prevalence of depression-related disorders among patients with pancreatic cancer is estimated to be as high as 71%.\textsuperscript{43} Moreover, numerous reports have documented the presence of depressive symptoms in patients before their pancreatic cancer was diagnosed.\textsuperscript{44-46} Recent physiological findings provide further evidence of a causal link between pancreatic cancer and depression. Pancreatic tumors secrete various neuropeptides and neurohormones such as adrenocorticotropic hormone (ACTH) and cortisol.\textsuperscript{47,48} These findings are consistent with a wealth of data showing that hypercortisolemia, as evidenced by nonsuppression of cortisol after dexamethasone administration, is associated with major depressive disorder.\textsuperscript{49} Pancreatic tumors also secrete calcitonin. These secretions can result in hypercalcemia,\textsuperscript{50,51} a condition characterized by prominent symptoms of lethargy and fatigue.\textsuperscript{52} In addition, there is evidence that pancreatic tumors also secrete growth hormone,\textsuperscript{53,54} another substance associated with increased depressive symptoms.\textsuperscript{49}

Certain forms of cancer treatment might also be a direct cause of both fatigue and depression. Along these lines, attention has focused on biologic response modifiers such as the interferons and the interleukins. These agents are used increasingly to treat a variety of cancers, including renal cell cancer and melanoma, and to control chronic myelogenous leukemia. Administration of supraphysiologic doses of these substances has been associated with prominent depressive symptoms, including fatigue.\textsuperscript{53-57} The occurrence of these psychiatric side effects is consistent with research showing that elevated levels of both interferons and interleukins are present in psychiatric patients with major depressive disorder.\textsuperscript{56,58-61}

### What Are the Treatment Implications of the Relationship of Fatigue to Depression?

In the previous section, we reviewed evidence suggesting the existence of 3 different causal relationships between fatigue and depression in patients with cancer. One possibility suggested by prior research is that patients experience fatigue as part of an underlying mood disorder. A second possibility is that patients develop symptoms of depression as a result of experiencing disease-related or treatment-related fatigue. A third possibility is that the correspondence between fatigue and depression in patients with cancer is the result of a third factor such as high-dose interferon therapy or tumor secretions.

In this section, we examine how these causal mechanisms could have implications for the management of fatigue.

The situation in which fatigue is part of a mood disorder is perhaps the easiest to manage because therapy will revolve around treatment of the underlying primary psychiatric disorder. Treatment of major depressive disorder in patients with cancer typically involves both pharmacologic and nonpharmacologic therapies.\textsuperscript{62} The selection of a specific antidepressant is likely to be guided by the symptom presentation. For example, if sleep disturbance were one of the chief presenting symptoms of depression, an antidepressant with sedating properties (such as amitriptyline) would be preferred. If, however, the patient's depression were accompanied by problems with diarrhea, like with several gastrointestinal cancers, then an antidepressant with constipating properties (such as paroxetine) would be preferred. By and large, research indicates that serotonin selective reuptake inhibitors (SSRIs such as paroxetine, sertraline, and citalopram) and medications that inhibit primarily noradrenergic reuptake (SNRIs such as venlafaxine, bupropion, and the tricyclic antidepressants) are equally efficacious in the treatment of major depressive disorder.\textsuperscript{63-65} As depressed mood improves, the associated fatigue can also be expected to resolve.

The management of disease-related or treatment-related fatigue accompanied by depressive symptoms is more complex. This situation reflects, in part, the relative lack of empirically supported interventions for fatigue in patients with cancer. In the absence of a strong body of
empiric evidence, several authors have proposed preliminary guidelines for the management of fatigue based largely on clinical experience with patients with cancer and research with other patient populations (Fig. 1). According to these guidelines, efforts to manage fatigue should focus on correcting potential etiologies as well as relieving symptoms. Potentially correctable etiologies, besides depression, include anemia, infection, other symptoms (such as pain), and centrally acting medications (such as opioids). Symptomatic therapies could include pharmacologic as well as nonpharmacologic interventions. Several of the proposed symptomatic therapies for fatigue (physical exercise, psychostimulant medications, and antidepressant medications) also have antidepressant properties.

A growing body of evidence indicates that exercise might be effective at relieving fatigue in patients who are undergoing or recovering from cancer treatment. Positive changes in mood are a likely consequence of regular exercise. At least one study has documented that reductions in treatment-related fatigue among regular exercisers were accompanied by corresponding reductions in anxiety and, to a lesser extent, depressed mood. These findings suggest that the beneficial effects of exercise on fatigue in patients with cancer could, in part, be the result of the mood-enhancing properties of exercise.

There is evidence that psychostimulants (such as methylphenidate, dextroamphetamine, and pemoline) might be useful in relieving fatigue related to opioid-induced somnolence, neurobehavioral slowing, and depression in patients with cancer. Preliminary research suggests that these agents are also useful in relieving disease-related or treatment-related fatigue in patients with cancer. Specifically, 2 open-label studies documented improvements in fatigue among patients with advanced cancer treated with methylphenidate. In addition, one open-label study documented improvements in fatigue among patients with melanoma receiving interferon who were treated with methylphenidate and also instructed to exercise daily. The mechanisms by which psychostimulants relieve disease-related or treatment-related fatigue have yet to be identified. In particular, it is unclear whether the effects of psychostimulants on fatigue are related to or distinct from their mood-enhancing properties.

Recommendations regarding the use of antidepressant medications to relieve fatigue in patients with cancer are based largely on clinical observations that these agents can produce increases in energy disproportionate to any changes in mood. Accordingly, these agents might be indicated for patients who are not depressed but are experiencing disease-related or treatment-related fatigue. Controlled trials are needed to identify the specific antidepressant agents that are effective at relieving fatigue. A randomized study has documented the efficacy of paroxetine in preventing depression induced by high-dose interferon administered to patients with melanoma. Although fatigue frequently accompanies depression in patients treated with high-dose interferon, the study did not report results for the effects of paroxetine on fatigue. These positive findings for depression should encourage additional research to determine whether paroxetine is also effective in relieving fatigue in patients treated with high-dose interferon. Two other antidepressant agents that appear to merit study are venlafaxine and bupropion. This suggestion is based on clinical observations that these 2 agents have particularly energizing effects. Both agents appear to function similarly to psychostimulants in that their use

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**Correction of Potential Etiologies**

- **Depression or Anxiety**
  - Antidepressants
  - Anxiolytics
- **Pain or Nausea**
  - Antigens
  - Antidiarrheals
- **Anemia**
  - Exclude common causes
  - Severe anemia
  - Transfuse
  - Mild to moderate anemia
  - Consider epoetin alfa
- **Other Conditions**
  - Correct fluid/electrolytes
  - Give oxygen
  - Treat infection
  - Reduce or eliminate nonessential medications

**Symptomatic Therapies**

- **Pharmacological Intervention**
  - Antidepressants
  - Psychostimulants
- **Nonpharmacological Intervention**
  - Energy conservation and restoration
  - Physical exercise
  - Sleep hygiene
  - Stress management

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Figure 1. Algorithm for management of cancer-related fatigue.
is associated with increased synaptic levels of norepinephrine. These findings are consistent with animal and human studies suggesting that increased levels of norepinephrine and/or dopamine are associated with increased levels of cortical arousal. Like with the psychostimulants, it will be important to clarify whether any observed effects of these agents on fatigue are related to or distinct from their mood-enhancing effects.

The guidelines described here are also applicable to the management of fatigue and depression related to a third factor. To the extent that the etiology of these symptoms is identifiable and correctable, efforts should focus on correcting the underlying cause(s). Often, correction of the underlying etiology is not practical or feasible. For example, it might be inadvisable to discontinue interferon even though a patient has become severely fatigued and depressed during the course of therapy. Under these circumstances, management efforts should focus on symptomatic relief. In the absence of a strong body of empirical evidence, clinical experience suggests the use of agents that are likely to have beneficial effects on both fatigue and mood symptoms (activating antidepressants or psychostimulants). Clearly, this is an area in which controlled outcome studies are needed.

Conclusions

In this article, we addressed four issues regarding the relationship of fatigue to depression in patients with cancer. First, we identified conceptual similarities and differences between fatigue and depression. As noted previously, fatigue and depression can each be assessed as a single symptom, a cluster of symptoms, or a clinical syndrome. Overlap was present among all three approaches to measuring fatigue and both the symptom-cluster and clinical syndrome approaches to measuring depression. This overlap reflects the inclusion of fatigue within symptom-cluster and clinical syndrome approaches to measuring depression and the inclusion of certain symptoms of depression (such as difficulty concentrating) within symptom-cluster and clinical syndrome approaches to measuring fatigue. Important conceptual differences were also identified. Certain symptoms (such as recurrent thoughts of death and muscle tension) generally appear only in measures of depression, whereas other symptoms (such as post-exertional malaise) generally appear only in measures of fatigue. Moreover, the clinical syndrome measurement approaches include criteria intended to differentiate cancer-related fatigue from mood disorders.

A second aim of this article was to determine the extent to which fatigue co-occurs with depression in patients with cancer. A review of the literature indicated that research on this topic has been limited primarily to the use of either single-symptom or symptom-cluster measurement approaches. The average correlation observed across studies between fatigue and depression was relatively high. The magnitude of the correlations is consistent with the previously noted overlap between measures of fatigue and measures of depression. There is evidence, however, that this correspondence is not solely a function of overlap in measurement approaches. For example, correlations between measures of fatigue and depression remained relatively high even when items reflecting phenomena associated with fatigue were removed from measures of depressive symptomatology. These findings suggest that the two measurement approaches currently in use (the single-symptom and symptom-cluster approaches) are of limited usefulness in attempts to distinguish fatigue from depression. Clinical syndrome approaches to measuring fatigue and depression could be better suited to this task and merit further study.

A third aim of this article was to explore the causal relationships between fatigue and depression in patients with cancer. A review of the literature suggested the existence of three different causal mechanisms. First, there is evidence consistent with the view that patients with cancer could become depressed as a consequence of experiencing disease-related or treatment-related fatigue. Second, there is evidence suggesting that fatigue can develop in patients with cancer as a consequence of their becoming depressed. Third, there is evidence indicating that the correspondence of fatigue with depression could be the result of a common third factor. Examples of such a third factor include certain neoplasms (pancreatic cancer) and certain forms of cancer treatment (interferon therapy) that appear to be a direct cause of both fatigue and depression. The specific mechanisms by which these neoplasms and treatments give rise to both fatigue and depression are not well understood and need to be investigated further.

The fourth and final aim was to consider the
treatment implications of the relationship between fatigue and depression in patients with cancer. When evidence suggests that fatigue is the consequence of a psychiatric disorder, efforts to manage the fatigue typically focus on treatment of the underlying psychiatric disorder. Management of fatigue that is disease-related or treatment-related and accompanied by depression is more complex, owing, in part, to the relative lack of empirically validated interventions. Current guidelines,\textsuperscript{10,66} based largely on clinical experience and research with other patient populations, suggest that efforts to manage fatigue under these circumstances should focus on correcting potential etiologies and relieving symptoms. Several of the proposed symptomatic therapies (physical exercise, psychostimulant medications, and antidepressant medications) have antidepressant properties. These therapies could be particularly useful in managing fatigue accompanied by depression as well as fatigue and depression attributable to a common third factor (for example, treatment with high-dose interferon). Evaluating the efficacy of these therapies and understanding their mechanisms of action in relieving fatigue should be considered high priorities for future research.

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