Evidence Report on the Occurrence, Assessment, and Treatment of Fatigue in Cancer Patients

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To determine the occurrence of cancer-related fatigue, the methods used to assess it, and the efficacy of the available treatments, we performed literature searches that identified English-language publications on these topics. Twenty-seven studies were identified in which the quantitative estimation of the occurrence of cancer-related fatigue was an end point. Fifty-six were judged to be relevant to the assessment of fatigue, and 10 randomized controlled clinical trials of treatments of cancer-related fatigue were retrieved. The occurrence of cancer-related fatigue was found to range from 4% to 91%, depending on the population studied and the methods of assessment. Few population-based studies and no longitudinal studies of cancer-related fatigue have been performed. The methods of fatigue assessment were highly variable. Exercise programs show promise to prevent or treat fatigue in some subsets of cancer patients, and the use of epoetin alfa for correction of anemia has been shown to ameliorate fatigue. The number of subjects in the treatment trials was small and their methodologic quality was inconsistent. [J Natl Cancer Inst Monogr 2004;32:40–50]

The Office of Medical Applications of Research at the National Institutes of Health requested that the Agency for Healthcare Research and Quality, through its Evidence-Based Practice Center program, produce an evidence report for a State-of-the-Science conference on the topic of Symptom Management in Cancer: Pain, Depression, and Fatigue. The purpose of this report was to search for and summarize evidence on several key questions related to these symptoms. The symptoms and key questions were identified by the State-of-the-Science Conference planning committee composed of staff from the Office of Medical Applications of Research, and the National Cancer Institute; national experts on this topic, and the Evidence-Based Practice Center staff. The findings of this report pertaining to the occurrence, assessment, and treatment of cancer-related fatigue are summarized below.

Fatigue is the symptom reported most frequently by patients with cancer *(1).* It is also the symptom that is reported as the most distressing, and the one that causes the greatest amount of interference with daily life *(2).* Despite this, there remains little consensus regarding definitions of fatigue or optimal methods of assessing and treating fatigue in cancer patients. Fatigue in cancer patients is both a side effect of treatment and a consequence of the biologic effects of the cancer itself. Some of the mechanisms of fatigue (such as anemia) are well recognized and potentially treatable, but the pathophysiology of fatigue in general remains poorly understood, and hence few effective treatments are available. There has been progress, however. Cancer-related fatigue is beginning to be recognized as a valid clinical diagnosis. In 1998, the International Classification of Disease included criteria for fatigue; and in 2000, the National Comprehensive Cancer Network (NCCN) published guidelines for its management *(3).*

METHODS

This evidence report was based on a systematic review of the literature on cancer-related fatigue, produced to provide background information for the National Institutes of Health Office of Medical Applications of Research and for the National Cancer Institute for use in a State-of-the-Science Conference held in July 2002. A comprehensive search of the medical literature was conducted to identify relevant studies. Tables were compiled of study characteristics and results, and the methodological quality of the studies was appraised.

The report was structured to address the following questions: What is the occurrence (prevalence or incidence) of cancer-related fatigue? How is cancer-related fatigue assessed? What are the treatments used for cancer-related fatigue, and what is the evidence for their effectiveness?

Literature Search

National Library of Medicine staff performed two separate but linked searches in September 2001, one from Medline and another from several databases (Embase, PsychInfo, Biosis, Embase, NTIS, CINAHL, and Allied and Complementary Medicine) to identify English-language articles that dealt with assessment, occurrence, or treatment of fatigue in cancer patients.

Selection of Studies

We accepted all studies of patients with cancer (or cancer survivors) who had fatigue or who were assessed for fatigue. We placed no restrictions on the patients' age, gender, ethnicity, or the type or stage of cancer.

Many studies were identified in which the occurrence of multiple cancer-related symptoms was assessed. It was beyond the scope of this report to extract the data on fatigue from such studies. Therefore, only studies that assessed fatigue as their primary purpose were included. We excluded studies that used only general health-related quality-of-life instruments unless a specific fatigue subscale was part of the assessment tool. Clinical trials that reported fatigue as a toxicity of treatment were also excluded. Only randomized controlled trials were included for the topic of treatment of cancer-related fatigue.

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Reporting Data

Full articles for selected abstracts were retrieved and examined in detail for possible data abstraction and inclusion in the tables. These tables provided detailed information about the study design, patient characteristics, inclusion and exclusion criteria, sample size, methods of assessment, interventions, and outcomes. Where appropriate, we graded the studies according to the methodological quality and applicability of the study. A narrative description of individual studies was also performed.

Grading of Evidence for Randomized Controlled Trials

The evidence presented on the treatment trials was graded for internal validity and applicability.

RESULTS

Characteristics of the Studies Assessing Fatigue Occurrence

Our search strategy identified 27 studies *(4–30)* in which a defined end point was the quantitative estimation of the prevalence or incidence of cancer-related fatigue in a specified patient population (Table 1). The reported rates of fatigue ranged from 4% in breast cancer patients before receiving adjuvant chemotherapy to 91% in patients before bone marrow or stem cell transplantation. The extreme variability in the reported rates of fatigue probably reflects the heterogeneity of the subject populations and the different methods that were used to assess and define fatigue.

The number of subjects in these studies ranged from 24 to 1957 (median = 129). The majority of the studies were prospective; only three were retrospective *(8,10,11).* Five studies used a case–control design *(15,16,19,23,25),* two were population-based *(21,27),* and the remainder were cohort studies. Fifteen of the studies were performed in the United States *(4,6,7,8,10,11,14,15,17,18,20,21,27,28,30),* 10 in Europe *(5,9,12,13,16,19,23–26),* and two in Asia *(22,29).* Thirteen studies assessed patients receiving active cancer treatment *(4,5,7,8–10,12,14,15,17,18,24,30),* eight focused on cancer survivors *(11,13,16,20–23,27),* three focused on patients receiving supportive or palliative care only *(6,19,29),* and three had varied subject populations *(25,26,28).* Five studies specifically focused on breast cancer *(8,14,15,20,22),* four on lung cancer *(5,7,10,29),* two on prostate cancer *(18,24),* and one each on Hodgkin's disease *(16)* and rectal cancer *(30);* the remaining studies included patients with a variety of cancers.

A variety of instruments were used to measure cancer-related fatigue. In 18 of the 27 studies, a multi-item questionnaire with defined psychometric properties was used. The fatigue subscale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire was used in four studies *(5,19,24,25).* No other instrument was used in more than two studies. Three studies used telephone interviews *(11,21,27).* Nonvalidated *ad hoc* questionnaires were used in three studies *(6–8).* Other methods of assessment included visual analog scales *(9,14,19,24)* and a single question *(28).*

A variety of definitions of fatigue were employed, along with gradations (e.g., "moderate," "severe"). Several studies characterized fatigue as either present or absent *(4,5,9,28).* Other studies established criteria for fatigue on the basis of patients' scores on various fatigue instruments [e.g., a score of ≤6 on the Lee Fatigue Scale *(17)* or the Piper Fatigue Scale *(18)*].

In the five case–control studies, fatigue was defined relative to a population without cancer *(15,16,19,23,25).* For example, scores of cancer patients on the Fatigue Severity Scale were compared with controls. Cancer-related fatigue was defined as a score in excess of the 95th percentile of the control group *(25).* The RAND Health Survey 1.0 is an instrument for which national age- and gender-specific norms are available. In a cohort of 1957 breast cancer survivors, fatigue was defined as a score that fell in the disability/limitation range of the energy/fatigue subscale of the RAND survey *(20).*

Occurrence of Fatigue During Chemotherapy or Radiation Therapy

Four studies reported rates of fatigue in patients receiving chemotherapy, five during radiation therapy, and four in groups receiving either one treatment or the other, or both.

In the studies of fatigue in the setting of chemotherapy, variable prevalence rates were reported. Richardson and Ream studied 109 patients receiving various types of chemotherapy using daily Visual Analogue Scales assessing the extent of fatigue, the distress caused by it, and the effect of fatigue on social and work-related activities. They reported that 89% of patients had fatigue at some point *(9).* In a sample of 127 patients with small-cell lung cancer receiving chemotherapy, "fatigue and malaise" were assessed using items from a European Organization for Research and Treatment of Cancer Quality of Life Questionnaire *(5).* At baseline, 43% had moderate to severe fatigue. Interestingly, this level declined slightly to 30%–37% during treatment, but all other symptoms were relieved over this period, presumably because of a high rate of response to chemotherapy. Fatigue was therefore the most prominent symptom over the course of treatment. This is one of the few studies that attempted to determine the extent to which fatigue was related to treatment or to the underlying disease. In multivariate analysis, 43% of the variance in fatigue was ascribed to disease symptoms and 35% to toxicity of treatment.

In one of the few studies of incidence (as opposed to prevalence), fatigue was reported to increase from 4% before cycle 1 to 28% before cycle 4 in 54 women receiving adjuvant chemotherapy for breast cancer, and fatigue was greater in patients than in the controls at all time points *(15).* Gaston-Johansson et al. found a 91% prevalence of fatigue using a visual analog scale in women with breast cancer after chemotherapy and before autologous stem cell or bone marrow transplantation *(14).*

A wide range of fatigue occurrence is reported in patients receiving radiation therapy, perhaps reflecting varying diseases, patient populations, types of radiotherapy, and the use of a variety of fatigue assessment instruments. In a study of 96 patients with a variety of cancers, fatigue rates ranged from 65 to 93% during radiation and 14% to 46% at a 3-month follow-up using a nonvalidated questionnaire *(4).* Hickok et al. performed a retrospective chart review of 50 patients receiving radiation therapy for lung cancer. According to symptom checklists and progress notes, they found that 78% of patients suffered from fatigue at some point during treatment *(7).* Among 250 ambulatory patients receiving radiation therapy with curative intent for a variety of cancers, 40% were tired "most of the time," 33%

Table 1. Prevalence of fatigue in cancer patients*

Author, year, country (ref)	N	Population/Setting	Mean age (range)/ % male	Cancer type	Prevalence (methods of assessment)
King, 1985, USA *(4)*	96	During and post-XRT	(26–83 y) 52% M	Chest, head and neck, GU, GYN,	65–93% during XRT, 14–46% @ 3 mo, depending on type of cancer (Symptom Profile)
Hurny, 1993, Switzerland *(5)*	127	Chemotherapy	ND Gender ND	SCLC	43% moderate or severe at baseline, 30–37% during chemotherapy (EORTC)
Donnelly, 1995, USA *(6)*	743	Palliative care service	(61–70 y) 53% M	Various cancers	48% "clinically important fatigue" (questionnaire)
Hickok, 1996, USA *(7)*	50	XRT	63 y (37–78 y) avg 68% M	Lung cancer patients	78% experienced fatigue at some point during XRT (SCC)
Longman, 1996, USA *(8)*	307	Patients on chemotherapy, hormonal therapy or XRT	55 y (25–82 y) 0% M	Breast cancer, stage I–IV,	83%; 60.2% "problematic" (SEB)
Richardson, 1997, UK *(9)*	129	During chemotherapy	58 y (26–82 y) 44% M	Various	89% at some point during chemotherapy (VAS)
Sama, 1997, USA *(10)*	60		58.3 y (33–80 y) 0% M	Advanced lung cancer	56.7% had "serious" fatigue (SDS)
Vogelzang, 1997, USA *(11)*	419	Patients who had received chemotherapy or XRT	65 y 33% M	Various cancers	78% reported fatigue during treatment, 32% on daily basis (FCS)
Smets, 1998, The Netherlands *(12)*	250	Ambulatory patients receiving XRT with curative intent	64 ± 13 y 59% M	Various cancers	During XRT 40% were tired most of the time, 33% sometimes, 27% hardly ever. 44% were more fatigued after than before XRT, 26% were less fatigued, 30% no change (MFI)
Smets, 1998, The Netherlands *(13)*	154	Patients in remission after XRT	65 ± 12 y 57% M	Various cancers	51% recalled fatigue in first 3 mo after XRT (19% very much, 32% moderate). No significant differences in fatigue scores between cases and controls at 9 mo (MFI)
Gaston-Johansson, 1999, USA *(14)*	127	Patients after surgery and chemotherapy, before autologous stem cell or bone marrow transplant	45 ± 7.6 y 0% M	Stage II, III, and IV breast cancer	91% had fatigue (VAS, PFS, SF-36)
Jacobsen, 1999, USA *(15)*	54 cases 54 controls	Patients receiving adjuvant chemotherapy	51 ± 10 y 0% M	Breast cancer	4% of patients had severe fatigue before cycle 1, 28% before cycle 4. Patients had significantly more fatigue than controls at all time points (MSAS, POMS-F, FSI)
Loge, 1999, Norway *(16)*	459 cases 2214 controls	Patients after curative treatment: 38% XRT, 14% chemotherapy, 47% XRT + chemotherapy	44 ± 12 y 55% M	Hodgkin's disease	26% of Hodgkin's survivors were fatigued vs. 9% of male and 12% of female controls (Fatigue Questionnaire)
Miaskowski, 1999, USA *(17)*	24	Outpatient XRT for bone metastases	56.6 ± 13 y 50% M	Various cancers	79% had moderate or severe fatigue at bedtime and 48% on awakening (LFS)
Monga, 1999, USA *(18)*	36	XRT	66.9 y (55–79 y) 100% M	Localized prostate cancer	8% were fatigued prior to XRT, 25% at completion of XRT (PFS)
Stone, 1999, UK *(19)*	95 cases 98 controls	Palliative care units, no chemotherapy or XRT in >4 wk	67 y (30–89 y) 43% M	Patients with advanced cancer	75% had severe fatigue (>95th percentile of controls) (VAS, EORTC, FSS)
Bower, 2000, USA *(20)*	1957	Breast Cancer Survivors 1–5 y after diagnosis	55 y 0% M	Breast cancer	35% classified as fatigued (scores in disability/limitation range on RAND Health Survey 1.0)
Curt, 2000, USA *(21)* [same as Cella 2001*(27)*]	379	Patients post-chemotherapy or XRT	53 y 21% M	Breast cancer (62% of patients) and various others	76% had fatigue at least a few days per month during most recent chemotherapy, 30% had daily fatigue. (structured telephone interview)
Okuyama, 2000, Japan *(22)*	134	Post-surgery patients (77% mastectomy, 23% breast-conserving) 28.1% had had chemotherapy, 8.9% XRT	55.1 ± 10.3 y 0% M	Breast cancer patients stage 0–III,	56% were fatigued (CFS, questionnaire)
Servaes, 2000, The Netherlands *(23)*	85 cancer patients 16 chronic fatigue	Patients disease-free at a mean of 2.9 y after treatment	47.5 ± 14 y 56% M	Various cancers and treatments	29% had heightened and 19% severe fatigue (CIS)
Stone, 2000, UK *(24)*	62	Patients receiving hormonal therapy	69 y (55–80 y) 100% M	Prostate cancer, various stages	14% had "severe fatigue" at baseline, 17% at 3 mo (severe fatigue defined as >95th percentile on FSS in controls without cancer)
Stone, 2000, UK *(25)*	227 patients 98 controls	Patients receiving outpatient care or inpatient palliative care	66 y (30–89 y) 56% M	Early breast or prostate cancer, inoperable lung cancer, or advanced cancer	Severe fatigue (>95th percentile of control group on FSS): breast cancer 15%, prostate cancer 16% inoperable lung cancer 50%, palliative care patients 78%
Stone, 2000, UK *(26)*	576	Patients attending three regional cancer centers over a 30-day period	59 y (18–89 y) 37% M	Various cancers and stages	58% reported being "somewhat" or "very much" fatigued (FACT-F, questionnaire)
Cella, 2001, USA *(27)* [same as Curt 2000 *(21)*]	379	Patients post-chemotherapy or chemotherapy + XRT	53 y 21% M	Various cancers (50% breast)	17% met proposed criteria for cancer-related fatigue; 37% reported ≥2 wk of fatigue in preceding month (telephone interview)
Given, 2001, USA *(28)*	841		(>65 y) 55% M	Breast, colon, lung, prostate	26–33% had fatigue at 4 time points over 1 y (single question)
Okuyama, 2001, Japan *(29)*	157	Ambulatory patients with advanced lung cancer, no surgery, chemotherapy or XRT in past 4 wk	63.1 y (27–80 y) 71% M	Advanced lung cancer	51.3% had clinical fatigue, defined as interfering with at least one domain of daily life (CFS, FNS, questionnaire)
Wang, 2001, USA *(30)*	72	Patients receiving pre-op chemotherapy & XRT	56 ± 11 y 50% M	Locally advanced rectal cancer	At baseline, 26% had moderate and 18% severe fatigue; at end of treatment, 28% had moderate and 31% severe fatigue (BFI)

*XRT = radiation therapy; CIS = Checklist of Individual Strengths; EORTC = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; SCC = Symptom Control Checklist; SEB = Side Effects Burden; VAS = Visual Analogue Scale; SDS = Symptom Distress Scale; FCS = Fatigue Coalition Survey; MFI = Multidimensional Fatigue Inventory; PFS = Piper Fatigue Scale; SF-36 = Medical Outcomes Study Short Form-36; MSAS = Memorial Symptom Assessment Scale; POMS-F = Profile of Mood States-Fatigue; FSI = Fatigue Symptom Inventory; LFS = Lee Fatigue Scale; FSS = Fatigue Severity Scale; CFS = Cancer Fatigue Scale; FACT-F = Functional Assessment of Cancer Therapy-Fatigue; FNS = Fatigue Numerical Scale; BFI = Brief Fatigue Inventory.

were tired "sometimes," and 27% "hardly ever" *(12)*. Monga et al. found that 8% of 36 patients with localized prostate cancer were fatigued before radiation therapy, and 25% were fatigued at its completion *(18)*. In a cohort of 24 patients receiving radiation therapy for bone metastases, 79% had moderate or severe fatigue at bedtime, and 48% had this level of fatigue on awakening *(17)*.

The only study of fatigue in the setting of concomitant chemotherapy and radiation focused on 72 patients with rectal cancer. The rates of moderate to severe fatigue rose from 44% at baseline to 59% at the end of treatment *(30)*.

In a cohort of breast cancer patients receiving chemotherapy, radiation therapy, and other treatments, an 83% prevalence of fatigue (60.2% "problematic") was found in patients with stage I–IV breast cancer *(8)*.

Fatigue has also been evaluated in large, cross-sectional studies of patients with many different cancers undergoing a variety of treatments. In a study of 841 elderly patients (>65 years of age) with newly diagnosed breast, colon, lung or prostate cancer, 26%–33% were found to have fatigue over a 1-year period *(28)*. Stone et al. found that 58% of 576 outpatients with a variety of cancers were fatigued *(26)*.

Fatigue in Cancer Survivors

Bower et al., using the RAND Health Survey 1.0, found a 35% fatigue rate (scores in the disability/limitation range) in 1957 breast cancer survivors *(20)*. Cella et al. found a 17% rate of fatigue among 379 cancer survivors, using somewhat restrictive diagnostic criteria *(27)*. In Hodgkin's disease, a high (26%) incidence of fatigue was found in a cohort of 459 survivors at a mean of 12 years after treatment *(16)*. Okuyama et al. studied 134 patients with stage I–III breast cancer a mean of 789 days after surgery, plus chemotherapy or radiation in 28.1% and 8.9%, respectively. Fifty-six percent of these patients reported fatigue *(22)*.

Fatigue in the Palliative Care Setting

Donnelly et al. found a 48% rate of "clinically important" fatigue using a questionnaire in 43 patients on a palliative care service *(6)*. A prospective, case–control study compared 95 cancer patients on a palliative unit with age- and sex-matched volunteers. Seventy-five percent of the patients had severe fatigue, defined as being greater than the 95th percentile of the control group *(19)*.

Patterns and Correlates of Fatigue

A number of additional studies (not included in Table 1, as they do not report occurrence rates of fatigue) have examined the pattern or correlates of fatigue. Some of the key findings from this literature are reviewed.

Not surprisingly, fatigue has been found to correlate with impairments in health-related quality of life in patients receiving radiation therapy *(31,32)* or chemotherapy *(33)* and in long-term survivors *(20)*.

Several studies examined putative biological correlates of fatigue with generally negative results. In patients with lung cancer who were undergoing radiation therapy, substantial weight loss was observed, but neither weight loss nor a laboratory marker of impaired nutritional status (prealbumin) correlated significantly with fatigue *(34)*. In patients who underwent autologous bone marrow transplants for lymphomas, gonadal dysfunction was found to be common, but it was not associated with greater fatigue. Likewise, there was no correlation between fatigue and serum levels of inflammatory cytokines (interleukin 6, tumor necrosis factor, soluble tumor necrosis factor receptor) in these patients *(35)*. There was also an absence of correlation between fatigue and mild Leydig cell dysfunction in survivors of various hematologic malignancies *(36)*. Both fatigue and serum interleukin 1 levels were found to increase between weeks 1 and 4 in men receiving radiation therapy for prostate cancer, but no statistical correlation was possible *(37)*.

Cancer-related fatigue has been associated with psychosocial and demographic factors, other symptoms, and disease and treatment variables. A common theme in several studies is an association between psychological distress, and depressive symptoms in particular, and fatigue. At least in some contexts, current physical and psychological symptoms were found to correlate with fatigue, whereas disease and treatment variables did not.

In breast cancer survivors, the variance in fatigue has been examined as a function of disease and treatment variables, symptoms, and demographics. In a large case–control study of breast cancer patients, the type of adjuvant treatment (chemotherapy, radiation therapy, or both) did not predict fatigue levels. The only significant predictors were the current symptoms of depression and pain *(20)*. Similarly, Broeckel et al. *(38)* found that demographic, disease, and treatment variables were not significantly correlated with fatigue after adjuvant chemotherapy. Again, current symptoms and conditions were correlated with fatigue, in this case poor sleep, menopausal symptoms, catastrophizing as a coping mechanism, and psychiatric disorders *(38)*. A similar pattern was observed in a third study of breast cancer survivors: Fatigue was significantly correlated with current symptoms of dyspnea, insufficient sleep, and depression, but not with disease or treatment variables *(22)*. In contrast, Mast *(39)* and Woo et al. *(40)* found associations between prior chemotherapy and fatigue.

Evidence that fatigue may be related to psychological states and other symptoms has been presented in numerous other contexts. Correlations have been found between symptom distress, psychological distress, and fatigue, but not between disease variables and fatigue, in 121 women receiving radiation therapy for breast cancer *(41)*. Redecker et al. found that fatigue is closely tied to psychological factors, particularly depression, in 263 patients undergoing chemotherapy *(33)*. Akechi et al. examined the correlates of fatigue in 455 ambulatory cancer patients. Cancer site and performance status did not predict fatigue. Aside from demographic variables, depression was the only factor correlating with fatigue *(42)*. In 31 patients undergoing autologous stem cell transplants for breast cancer, there were no associations between fatigue and demographics, disease variables, or the transplant regimen. The factors that were associated with fatigue were time to engraftment, length of hospitalization, depressive symptoms, and anxiety *(43)*. In a study of 457 Hodgkin's disease survivors, anxiety was predictive of chronic fatigue *(44)*. Bruera et al. found that asthenia correlated with depression but not with nutritional status, lean body mass, tumor mass, anemia, or type of treatment in 64 patients with advanced breast cancer *(45)*.

Assessment of Cancer-Related Fatigue

The literature search yielded 176 abstracts related to the assessment of fatigue. More than 100 papers were retrieved and reviewed. Preliminary screening resulted in the elimination of almost half, and ultimately 56 papers were judged to be relevant *(12,14–16,18,19,22,23,31,32,38–40,42,44,46–86).*

The number of subjects in these studies ranged from 14 to 987, with a median of 92. Twenty-six of the studies were performed in the United States and Canada, 23 in Europe, four in Asia, and two in Australia. Almost all studies were of adults; only one was of children (ages 10–18 years). The instruments used for fatigue assessment are presented by disease type in Table 2. Some of these studies used instruments that are very specific to cancer-related fatigue, such as the Piper Fatigue Scale and the Brief Fatigue Inventory, whereas in other studies fatigue subscales from more general quality-of-life instruments were used. The majority of these studies were performed for the purpose of developing and testing patient self-report instruments for the assessment of fatigue. These efforts have led to the availability of several sophisticated research tools that measure multiple dimensions of fatigue and that are consistent, reliable, and valid in many patient populations.

Treatment of Cancer-Related Fatigue: Methodological Issues

The literature search identified 10 randomized controlled trials assessing the efficacy of various interventions for the treatment of cancer-related fatigue (Table 3) *(87–96).* The majority of these trials were small (median 70.5 subjects); only two included more than 100 subjects. Six trials were conducted in single institutions and three in multiple institutions. In one trial *(87),* the number of institutions could not be determined.

Reporting of elements of the study design, such as primary and secondary end points, sample size calculation, eligibility criteria, and procedures for randomization and stratification was inconsistent. An important and recurrent issue in the design and reporting of these trials is the absence of prospectively defined quantitative end points. Among the 10 trials, only one provided a clear definition of end points *(96).* The absence of prospectively defined end points was problematic in studies that measured and reported numerous outcome variables. For example, in a study of the effects of massage therapy on anxiety, depression, and mood in bone marrow transplantation patients, the State-Trait Anxiety Inventory, Beck Depression Inventory, and Brief Profile of Mood States were administered. Fatigue was found to be statistically significantly lower in the massage group at two of the three time points ($P = .02$ at day -7, and .03 predischarge) *(91).* However, these fatigue scores were only two of 36 dependent variables (12 variables at three time points), each of which was assessed for statistically significant differences between the treatment and control group. Among so many potential outcomes, the post hoc selection of the few variables with P values less than .05 is difficult to interpret.

Similar problems arise in interpreting the results of a study evaluating a Comprehensive Coping Strategy Program (CCSP) in patients undergoing autologous bone marrow transplantation for breast cancer *(93).* The effects of this program on pain, fatigue, psychological distress, and nausea were assessed using a number of questionnaires and visual analogue scales at three time points. This generated 24 outcome variables. Of these, only the measurements of nausea at day $+7$ and fatigue at day $+7$ correlated significantly with the CCSP. It is difficult to interpret the few outcomes that correlate significantly with CCSP in light of the large number of outcomes reported, the absence of a prospective definition for which these outcomes was of primary interest, and an estimation of the effect size that would have been considered clinically important.

Because end points were not defined prospectively in the majority of these trials, calculations of the sample size required for detection of significant outcome differences could not be performed. With a few exceptions, the sample sizes appear to have been chosen arbitrarily. It is therefore possible that some of

Table 2. Fatigue assessment instruments: use by cancer type

Cancer type	EORTC	VAS	MFI	POMS	FACT	PFS	GLQ-8	RFS	SDS	FSC	PBFFC	SF-36	Total
Breast	5	5	4	4	1	4	1		2	1	2	1	30
Lung	3	5	2	2	1		1	1	1	1			17
Prostate	2	3	4	1		1		1					12
Gynecologic	2		3	2	1		1						9
Lymphoma	1		3	1	1		1	1	1				9
Colorectal	1	2		1	1			1					6
Gastrointestinal	1	3	1	1									6
Hodgkin's	2	1	1										4
Melanoma	1			1		1			1				4
Myeloma	1	2								1			4
Head and Neck			1	1									2
Leukemia					1			1					2
Brain				1									1
Liver				1									1
Oral	1												1
Skin	1												1
Stomach				1									1
Testicular							1						1
Bladder													0
Total	21	21	19	17	6	6	5	5	5	3	2	1	

EORTC = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; VAS = Visual Analogue Scale. MFI = Multidimensional Fatigue Inventory; POMS = Profile of Mood States; FACT = Functional Assessment of Cancer Therapy; PFS = Piper Fatigue Scale; GLQ-8 = Global Quality of Life-8; RFS = Rhoten Fatigue Scale; SDS = Symptom Distress Scale; FSC = Fatigue Symptom Checklist; PBFFC = Pearson Byars Fatigue Feeling Checklist; SF-36 = Medical Outcomes Study Short Form-36.

Table 3. Randomized clinical trials of treatment of fatigue in cancer patients*

Author, year (ref)	N	Treatment (patient population)	Effect	Methodological quality†	Applicability‡
Spiegel, 1981 *(87)*	86	Weekly support group for 1 y (metastatic breast cancer)	Declines in vigor and increasing fatigue were seen in control group but not in the treatment group ($P<.01$). Those who participated in weekly group session for one year had significantly lower scores on POMS fatigue subscale.	C (Unblinded, high drop-out)	B (Metastatic breast cancer only)
Forester, 1985 *(88)*	100	Psychotherapy (patients undergoing XRT)	SADS administered at baseline, near midpoint of XRT, at end of XRT and 4 wk and 8 wk post-XRT. Only at 4 wk post-XRT was there a significantly greater change from baseline fatigue scores in the therapy group compared with control group.	C (Unblinded, significant difference in fatigue at only one of multiple time points)	I
Decker, 1992 *(89)*	82	Relaxation therapy (patients undergoing XRT)	Treatment group had a nonsignificant change in fatigue score over the course of treatment, whereas in controls, fatigue increased significantly.	C (Unblinded, minimal baseline patient information	I
Mock, 1997 *(90)*	46	Exercise (early stage breast cancer patients undergoing XRT)	Exercise group scored significantly higher than usual care group on physical functioning ($P = 0.003$) had lower symptom intensity, especially fatigue.	B (Unblinded)	B (Early stage breast cancer only)
Ahles, 1999 *(91)*	34	Massage vs. quiet time (BMT)	Borderline significant results for fatigue ($P = 0.06$). Most robust effects at day 7 assessment (first week of treatment).	C (Unblinded, primary endpoint not defined)	B (BMT patients only)
Dimeo, 1999 *(92)*	59	Aerobic exercise (stationary biking) vs. control (PBSCT)	No significant differences were present at baseline; control group had significantly more fatigue at discharge compared with baseline ($P<0.02$), exercise group did not.	B (Unblinded)	B PBSCT patients only)
Gaston-Johansson, 2000 *(93)*	110	Comprehensive Coping Strategy Program vs. usual care (BMT)	Fatigue significantly less in treatment group compared with control at day 7. Significance disappears in multivariate analysis when controlled for demographic variables and fatigue at day 2.	B (Unblinded primary endpoint not defined)	B (BMT patients only)
Oyama, 2000 *(94)*	30	Bedside Wellness System using virtual reality vs. usual care (chemotherapy)	There was a statistically significant difference between level of fatigue in treatment and control groups after two treatments, but not after one.	C (Unblended, minimal baseline patient information)	A (Patients undergoing chemotherapy)
Mock, 2001 *(95)*	48	Walking program vs. usual care (early stage breast cancer, XRT and/or chemotherapy)	Fatigue scores did not differ significantly between exercise and usual care groups at end of treatment. Many in control group exercised, confounding results.	C (Unblinded, confounded by compliance issues)	B (early stage breast cancer only)
Littlewood, 2001 *(96)*	251	Epoetin alfa vs. placebo (patients receiving chemotherapy)	There was a strong statistically significant correlation between hemoglobin levels and QOL. The mean increase in hemoglobin level from baseline to last value was significantly greater in the epoetin alfa group than the placebo group (2.2 g/dL vs. 0.5 g/dL, $P<0.001$). Significant differences observed for epoetin for all five cancer and anemia-specific primary QOL measures ($P\leq.0048$)	A	A

*BMT = bone marrow transplantation; PBSCT = peripheral blood stem cell transplantation; QOL = quality of life; XRT = radiation therapy.

†Clinical trials were graded on scales of internal validity as follows. A = Least bias: double-blinded, well-concealed randomization, few drop outs, and no (or only minor) reporting problem of the trial that is likely to cause significant bias. B = Susceptible to some bias: single-blinded only, unclear concealment of randomization, or has some inconsistency in the reporting of the trial but is unlikely to result in major bias. C = Likely to have large bias: unblinded study, inadequate concealment of random allocation, high dropout rate, or has substantial inconsistencies in the reporting of the trial such that it may result in large bias.

‡Clinical trials were graded on scales of applicability as follows (unable to assess internal validity due to lack of reported information). A = High degree of applicability: patients enrolled in the trial represent a broad spectrum of the population. B = Restricted applicability: the study included only a narrow/restricted study population, but the result is relevant to similar types of patient populations. C = Very limited direct applicability or not applicable: the study population was not comparable to any relevant patient population, or the study reported only limited information. I = Uncertain applicability: not reported or insufficient information to assess external validity issues.

the reported negative outcomes were to the result of inadequate statistical power of the studies.

The patient populations in several of these trials were quite heterogeneous. Six of the 10 trials enrolled patients with multiple types of cancer. For example, Decker et al. studied the effects of relaxation therapy in 82 patients with 15 different types of cancer who were undergoing palliative or curative radiation therapy *(89)*. Patient factors such as performance sta-

tus, disease factors such as stage, and treatment factors such as dose and anatomic sites of radiation therapy were probably highly variable in this group. These factors may have accounted for much of the variance of fatigue. Stratification to ensure balance of such factors between the arms of the study would have been a reasonable approach in many of these trials, but only two of the more recent studies stratified patients *(95,96).* Particularly in earlier trials, minimal demographic, disease, and treatment information is provided.

Treatment of Cancer-Related Fatigue: Results of Randomized Controlled Trials

Several trials evaluated the effect of psychosocial interventions on fatigue. Spiegel et al. randomly assigned 86 women with metastatic breast cancer to either usual care plus weekly support group meetings for 1 year or usual care alone *(87).* Despite a high drop-out rate (only 54 patients were evaluable and only 30 remained at the end of 1 year), the support group arm had significantly better scores on multiple dimensions of the Profile of Mood States, including less fatigue and more vigor. Over the course of the year, controls showed increasing fatigue and declining vigor, but this result did not occur in the treatment group *(87).* Despite flaws in this study, the consistent benefit associated with support group attendance across multiple dimensions of the Profile of Mood States is striking and is certainly consistent with more recent data on the benefits of support groups.

Forester et al. examined the effect of psychotherapy in patients receiving radiotherapy *(88).* Forty-eight patients were randomly assigned to weekly psychotherapy for 10 weeks during and after radiation, and 52 to radiation alone. The groups were reasonably well balanced according to basic demographics and type of cancer. Subjects were administered the Schedule of Affective Disorders and Schizophrenia at five time points from baseline to 14 weeks. Psychotherapy patients had a significantly greater decline in emotional symptoms than controls from the end of radiation to the final time point. Physical symptoms, and fatigue in particular, declined more in the treatment group, but they only reached statistical significance at one time point *(88).* Although this study is by no means definitive, it is consistent with other data that indicate a strong influence of psychological state (and possibly psychological intervention) on fatigue.

Some of the problematic features of a trial of relaxation therapy during radiation therapy *(89)* have been discussed above. The sample was highly heterogeneous, and only rudimentary patient information was provided. Significant baseline differences in all subscales of the Profile of Mood States indicate that the arms were poorly balanced for factors associated with psychological symptoms and fatigue. Although fatigue remained stable in the relaxation therapy group and increased significantly in the control group, the validity of these results is questionable.

A CCSP was compared with usual care in patients undergoing bone marrow transplantation *(93).* The CCSP consists of counseling, education, written materials, and an audio tape providing information on pain control and its importance, mechanisms of pain, strategies for reducing pain and emotional distress, coping skills, cognitive restructuring to avoid catastrophizing, and demonstration and instruction in guided imagery and relaxation. The groups were well balanced for demographic and disease variables. As noted above, several instruments were used to assess psychological distress, fatigue, nausea, and pain. Although a few statistically significant correlations were found between participation in the CCSP and reduced symptoms at certain time points, the evidence for a clinically meaningful benefit from this approach is preliminary.

Three studies examined the effects of exercise on fatigue in breast cancer patients. Mock et al. randomized 46 women undergoing radiation therapy for early stage breast cancer to an individualized, home-based walking exercise program or usual care *(90).* The outcomes were physical functioning (measured by a 12-minute walking test), and scores on the Symptom Assessment Scale and Piper Fatigue Scale, administered at the midpoint and end of radiation therapy. The patient sample was relatively small but homogeneous, and they underwent a fairly uniform treatment (radiation therapy for localized breast cancer). The groups were well balanced demographically and by disease factors, and there were no significant differences in the baseline levels of fatigue or other symptoms. All patients experienced fatigue. There were highly significant differences in the pre- to post-test values in physical functioning, exercise level, fatigue, difficulty sleeping, and anxiety, all favoring the treatment group. At the end of radiation treatment, when fatigue is typically most intense, the exercise group was significantly less fatigued. A similar study by Mock et al. assessing exercise in both chemotherapy and radiation patients was confounded by the fact that a high percentage of the control group participated in exercise, whereas compliance in the treatment group was low *(95).* Dimeo et al. found that in patients undergoing autologous peripheral blood stem cell transplantation, daily biking on an ergometer in the supine position was associated with stable levels of fatigue at discharge compared with admission, whereas in a control group, fatigue levels rose significantly *(92).*

Littlewood et al. performed the only randomized, placebo-controlled trial showing a benefit for a pharmacological intervention in cancer-related fatigue *(96).* They randomly assigned patients receiving nonplatinum chemotherapy to thrice-weekly subcutaneous epoetin alfa (n = 251) or placebo (n = 124) in double-blind fashion. Patients had hemoglobin levels of $\leq$10.5 g/dL, or 10.5–12 g/dL with a decline of $>$1.5 g/dL per cycle of chemotherapy. Patients were stratified according to solid versus hematologic malignancies and hemoglobin level. This study was appropriately powered to detect the primary end point (the proportion of patients transfused after 4 weeks). Secondary end points were change in hemoglobin level, percentage of patients with an increase in hemoglobin of $\geq$2 gm/dL, and change in quality of life scores from baseline to last value. Quality of life was assessed using the Functional Assessment of Cancer Therapy–Anemia, which contains a fatigue subscale; the Linear Analog Scale Assessment; and the Medical Outcomes Study Short Form-36. Transfusion requirements were significantly lower and hemoglobin levels significantly higher on the epoetin alfa arm. All quality-of-life measures also showed a benefit. There was a highly statistically significant difference in the mean change in fatigue subscale scores on the Functional Assessment of Cancer Therapy–Anemia, favoring epoetin alfa ($P = .0040$). Changes in hemoglobin levels strongly correlated with quality of life. There also was a trend toward improvement in overall survival in the epoetin group. These results are consistent with two large open-label nonrandomized studies of epoetin alfa that also demonstrated benefits in terms of hematologic parameters, quality of life, and measurements of energy and fatigue *(102,103).* An-

other nonrandomized study has indicated that anemic cancer patients not currently receiving chemotherapy may also benefit from epoetin alfa in terms of amelioration of anemia and improvement in quality of life *(104)*.

Discussion

Occurrence of Cancer-Related Fatigue

Estimations of fatigue occurrence have been performed in many settings, but the data are by no means comprehensive. Many types of cancer were not specifically addressed. Most studies were conducted at academic centers and used relatively small and possibly highly selected cohorts of patients. It is therefore possible that the most fatigued patients were unable to participate. A number of larger case–control or population-based studies have also been performed that may be less subject to selection bias *(15,19,20,24,25,27)*.

The period over which the prevalence of fatigue was assessed in any group of patients was short—generally confined to the period of treatment and immediately after, or one time point in studies of survivors. No studies have tracked the time course of fatigue longitudinally using a uniform methodology. Few studies on the prevalence of fatigue reported data on factors that might contribute to fatigue (such as anemia, infections, etc.) or attempted to determine to what extent fatigue was to the result of treatment, disease, or other factors.

A very broad range of occurrence rates were reported, but comparisons of the rates in these studies are problematic, as virtually all published studies have used different criteria for defining fatigue and grading its severity.

Assessment of Cancer-Related Fatigue

The literature on fatigue assessment focuses on tools that are used in research studies, and to a much lesser extent on methods of assessment for clinical use. In the context of clinical research, assessment of fatigue involves the use of patient self-report instruments of varying levels of complexity. Most studies in the last several years have used instruments that assess multiple dimensions of fatigue and have been tested for validity, consistency, and reliability. Issues still remain in terms of the clinical interpretation of the scores obtained on these instruments and the comparison of fatigue measurements obtained using different instruments.

The NCCN has published guidelines for the assessment and management of cancer-related fatigue. The approaches recommended are for the most part not based on randomized controlled trials, but reflect the opinion and experience of a panel of experts. It would be useful to know the extent to which causes of fatigue can be identified and reversed using these algorithms.

Treatment of Cancer-Related Fatigue

Ten randomized, controlled trials were identified that assessed interventions for cancer-related fatigue. Four involved psychosocial interventions *(87–89,94)*. Three clinical trials evaluated the effect of exercise on fatigue *(90,92,95)*. One trial involved massage therapy *(91)*, and one evaluated a "bedside wellness system" using virtual reality technology *(94)*. There was only one trial of pharmacotherapy (epoetin alfa for fatigue related to anemia in patients receiving chemotherapy) *(96)*. End points were poorly defined and sample size calculations were absent in several of these studies. It is possible that many of these studies were inadequately powered to detect the outcome of interest. Although several studies reported statistically significant associations between the intervention being tested and various outcomes, the absence of prospectively defined end points renders these results difficult to interpret.

Studies by Mock et al. *(90)* and Dimeo et al. *(92)* provide evidence that exercise may be helpful in reducing or preventing fatigue in patients receiving radiation therapy for early stage breast cancer, and in those undergoing bone marrow transplantation. These studies were small, and the beneficial effects of exercise are less clear in other contexts, but exercise is certainly an approach that warrants further investigation. Several nonrandomized studies have also reported beneficial effects of exercise on cancer-related fatigue *(97–101)*.

The randomized, placebo-controlled, double-blind trial by Littlewood et al. *(96)* suggests a benefit associated with epoetin alfa in terms of quality of life, fatigue, and hematologic parameters in anemic patients undergoing chemotherapy. The findings of this study are supported by large, nonrandomized trials. No other randomized controlled trials of pharmacotherapy for cancer-related fatigue were identified. Psychostimulant medications, which have been shown to ameliorate fatigue in AIDS patients *(105)*, are currently undergoing clinical trials in cancer patients.

Recommendations for Clinical Management and Future Research

Fatigue is a pervasive and debilitating problem in cancer patients and survivors. Therefore, an assessment of fatigue should be part of the routine clinical evaluation of these patients. The NCCN practice guidelines on cancer-related fatigue (3) (http://www.nccn.org/physician_gls/f_guidelines.html) recommend the use of simple 0–10 numerical self-report scales or verbal scales (e.g., mild, moderate, or severe) to assess the severity of fatigue. If moderate or severe fatigue (a score of 4–10) is reported, the NCCN panel recommends a focused history and physical examination and evaluation of the pattern of fatigue, associated symptoms, and interference with normal functioning. Potentially reversible causes of fatigue should be assessed, including pain, emotional distress, sleep disturbance, anemia, and hypothyroidism. The possibility of depression should be carefully considered, given its high prevalence in cancer patients. Although this algorithm is based on the experience of a panel of experts and is intuitively reasonable, it has not been evaluated prospectively.

It is probable that a substantial burden of fatigue will persist in many patients even after attempts to identify and treat reversible causes. What can be done for these patients? A number of interventions can be considered, even if the evidence from randomized clinical trials is sparse or nonexistent. Patients should be offered reassurance that fatigue is common and does not necessarily indicate cancer progression. Exercise has been shown to ameliorate fatigue in patients with early-stage breast cancer. It is reasonable to recommend exercise or physical therapy to other subsets of patients (although with caution in patients with bone metastases or cytopenias). Strategies for energy conservation or psychosocial interventions may be helpful for some patients. A trial of a psychostimulant medication,

antidepressant, or corticosteroid may be considered, although the data to support their effectiveness in treating cancer-related fatigue are very limited, and all these treatments have potential side effects.

Our structured review of the literature on cancer-related fatigue led us to identify certain areas in which future research should focus. The proliferation of instruments used to assess fatigue makes comparison of studies problematic. Investigators should use validated, reliable instruments for fatigue assessment, and efforts should be made to correlate these instruments and to clarify their clinical relevance. Longitudinal studies are needed to assess the time course of fatigue in cancer patients and survivors. Although the occurrence of fatigue in some subsets of patients has been the subject of numerous studies, other groups, notably pediatric cancer patients, have been almost entirely neglected. A prospective study to validate the effectiveness of the NCCN guidelines for assessing and treating cancer fatigue would be of great interest. In particular, it would be useful to know the extent to which fatigue can be ameliorated by identifying and treating various contributing factors.

Further basic research is needed on the pathophysiology of cancer-related fatigue, including the development of animal models to study the role of cytokines, nutritional factors, muscle wasting, and other putative etiologic factors. Studies correlating such factors with fatigue in cancer patients are also needed to develop rational hypotheses for treatment trials.

Several promising approaches to treatment of fatigue have been identified on the basis of preliminary clinical trials or clinical experience. These approaches require further investigation in randomized, controlled trials. Among the more promising treatments are exercise programs, psychosocial interventions (with a particular focus on the detection and treatment of depressive symptoms), and the use of stimulant medications. Other potential treatment approaches that warrant preliminary laboratory investigations or pilot trials include hormonal treatments such as human growth hormone, androgens, antiinflammatory medications, L-carnitine, and dietary interventions. Future clinical trials for cancer-related fatigue should use appropriate study designs, including prospectively defined end points. They should have adequate statistical power to detect differences in the end points of interest. The development of strategies to overcome obstacles to accrual in studies of cancer symptoms should be a priority.

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