Assessment and management of cancer-related fatigue in adults

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Fatigue is one of the most prevalent and distressing symptoms of cancer, and is a common side-effect of many of the treatments available for the management of malignant disease. We critically assess the evidence for cancer-related fatigue and its treatment in adults. Little is known about the cause and mechanisms of fatigue, and research into methods of alleviating the condition has focused on treatment for anaemia and behavioural interventions, such as exercise, both of which are effective in reducing fatigue. Although research into the condition has increased considerably in the past decade, important gaps in knowledge remain.

70–100% of patients being treated for cancer are affected by cancer-related fatigue, which can be more distressing and disruptive to daily activities than the pain associated with the disease. However, individuals are often reluctant to report fatigue, and cancer-care providers frequently do not screen for it because they are uncertain about how to treat the condition. Evidence suggests that high degrees of fatigue during treatment can lead to significant reductions in physical functioning and quality of life, yet its causes remain poorly understood.

We detail the prevalence and possible causes of fatigue, and critically assess methods for its assessment and management. The symptoms, as well as the distress associated with, and consequences of, cancer-related fatigue are also discussed. Finally, we identify what further research is needed.

Definition
Cancer-related fatigue, defined by the National Comprehensive Cancer Network (NCCN) as “a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning,” can be described in terms of perceived energy, mental capacity, and psychological status. It arises over a continuum, ranging from tiredness to exhaustion. But, by contrast with the tiredness sometimes felt by a healthy individual, cancer-related fatigue is perceived as being of greater magnitude, disproportionate to activity or exertion, and not completely relieved by rest, leaving the patient with an overwhelming and sustained sense of exhaustion. Fatigue is an umbrella term used to describe various sensations or feelings, and a variety of expressions of reduced capacity at physical, mental, emotional, or social levels. How cancer-related fatigue is related to indicators of tiredness, such as reduced energy expenditure, sleep disturbance, attention deficits, decreased endurance, and weakness, is unclear.

Incidence
Fatigue is the most prevalent symptom of individuals with cancer who receive radiation therapy, cytotoxic chemotherapy, or biological response modifiers. In one study, 75% of patients with various solid tumours (in which 48 of 95 had metastatic disease) had a significantly increased fatigue score by comparison with a matched control population. Furthermore, individuals who survive cancer report fatigue as a problem months to years after treatment ends. In a survey of 1957 survivors of breast cancer, for example, a third reported severe and persistent fatigue 3 years after diagnosis.

The patient’s perspective
In healthy individuals, fatigue generally serves as a protective or pleasant response to physical or psychological stress. For patients with a chronic disease, however, it can become a distressing symptom, which negatively affects daily functioning and quality of life.

There is little information with respect to the meaning, effect, and experience of cancer-related fatigue from the patient’s perspective, although a few qualitative studies have been done. The results of these studies indicate that fatigue affects the whole person—ie, their body and mind—and is a complex symptom with physical, emotional, and mental effects. Patients have variously described themselves as feeling listless, sluggish, faint, apathetic, tired, slack, indifferent, and having paralysing fatigue.

Search strategy and selection criteria
We did a search of work published between January, 1997, and October, 2002, using the following databases: Medline, Cancerlit, Cinahl, and the Cochrane Library. We also consulted some classic work published before 1997. Abstracts from the past 5 years of meetings of the American Society of Clinical Oncology (ASCO) and the European Cancer Conference (ECCO) were reviewed. Only studies published in English and done in adults have been included. The key words used in searches were: assessment, cancer, chemotherapy, definition, evaluation, experience, fatigue, immunotherapy, intervention, management, measurement, quality of life, radiotherapy, and symptom distress.
Cause
The specific mechanisms involved in the development of cancer-related fatigue are not completely known, but both physiological and psychosocial factors play a part.

Physiological factors
Physiological factors that contribute to the development of fatigue include anaemia, cancer therapy, cachexia, tumour burden, and the release of cytokines, in the order of the amount of evidence available.

Anaemia
Haemorrhage, haemolysis, and nutritional deficiencies, as well as the increased production of cytokines, which counteract the differentiation of erythroid precursors, reducing the production of erythropoietin, and hence contributing to impaired iron use, are all potential causes of cancer-associated anaemia.5 Cytotoxic chemotherapy and radiation therapy can also contribute to anaemia.27

In an assessment of 2719 patients, receiving chemotherapy in centres in the UK, 33% needed at least one blood transfusion for anaemia.5 A review5 of the published work on chemotherapy-induced anaemia in adults reported that the highest anaemia rates arose in patients with lung, gynaecological, and genitourinary tumours, with incidences of 50–60%.

Fatigue is the most frequent manifestation of anaemia in patients with cancer.28 30 However, many patients who are not anaemic, also report high degrees of debilitating fatigue.29

Treatment
Findings of studies35,36 indicate that fatigue increases during radiation therapy, such as for prostate cancer and lung cancer, and in relation to chemotherapy and hormonal therapy,30 especially in the setting of adjuvant breast cancer, in which the patient is generally asymptomatic before initiation of treatment.31 Fatigue is also reported by 70–100% of patients who receive interferon. In this last instance cancer-related fatigue is a dose-limiting side-effect, which is mediated by neuroendocrine dysfunction.32

There is little published work with respect to why certain treatments cause fatigue. One important factor could be the decline in haemoglobin concentrations that can occur with some chemotherapy33 or radiation therapy protocols.34 However, in a phase III trial of epoetin alfa, stable haemoglobin values were reported for the placebo group despite worsening of fatigue scores during chemotherapy,35 and in another study, haemoglobin values did not change in women treated with radiation therapy for breast cancer, but fatigue scores increased.36 Clearly, the mechanisms of fatigue related to cancer treatment are multiple. It is noteworthy, though, that fatigue and other symptoms can improve in patients with metastatic disease if the cancer responds to therapy.37

Cachexia
Cancer-related cachexia is often included in lists of contributory factors for the development of fatigue. Cytokines, which accumulate as a by-product of cellular damage and destruction, might interfere with the hypothalamic control of hunger and mediate the development of cachexia.38,39 Fatigue might also be induced by loss of nutrients as a result of anorexia, nausea, vomiting, or hypermetabolism.

Few prospective studies have investigated the effect of improvements in nutritional state on degree of fatigue. However, through the interference of eicosanoids, cyclooxygenase inhibitors decrease tumour growth and improve energy balance in animals40 and in people.41 Furthermore, results of a trial in patients with advanced lung cancer showed that infusion of ATP greatly improved energy status and quality of life.42 Effective interventions against cancer-related cachexia could, hypothetically, therefore also have beneficial effects on fatigue.

Tumour burden
Although it seems reasonable to assume that the extent of tumour bulk or presence of metastatic disease will affect the degree of fatigue, findings of several studies43 44 indicate no correlation. These studies, however, all involved only small numbers of patients, and two studies that collectively analysed individuals with different types of tumours did report an association.15 45 In the first study,47 comparing four groups of patients recently diagnosed with breast, prostate, or inoperable non-small-cell lung cancer, or receiving inpatient palliative care, the two latter groups had a higher degree of fatigue than did the two former groups. A significant correlation between disease burden and fatigue was also noted. Furthermore, in a study of elderly patients newly diagnosed with different cancers, clinical stage (early vs late) was associated with extent of fatigue and pain.46 Thus, overall, the results of these studies lend support to the notion that tumour stage is associated with degree of fatigue.

Cytokines
In some instances, cytokines—proteins that mediate cell-to-cell communication—are released in greater amounts in cancer patients than in healthy individuals. This cytokine release could contribute to the development of fatigue by exerting effects on the endocrine system and neurotransmitters,48 for example, as suggested in chronic fatigue syndrome.49 High concentrations of tumour necrosis factor α (TNF-α), interleukin 1, and interleukin 6 have been described in various cancers, and can contribute to fever, weight loss, sweats, and anaemia, as well as fatigue.49 50

Descriptive research, however, has focused mainly on the correlation of these factors with disease stage or prognosis, both in solid tumours and in haematological malignant diseases.51 61

The cytokine cascade can be initiated by radiation therapy, since irradiated monocytes and macrophages secrete cytokines—eg, interleukin 1, interleukin 6, and TNF-α. Therefore, cytokine concentrations during treatment have been studied. In a trial of 15 men who received radiation therapy for localised prostate cancer, serum concentrations of interleukin 1 rose as fatigue levels increased.42 However, values for interleukin 1, interleukin 6, and TNF-α did not rise in 41 women who received local radiotherapy after breast-conserving surgery.52 Furthermore, in a follow-up study of 32 patients treated with high-dose therapy for malignant lymphoma, an increased degree of fatigue was noted, but concentrations of interleukin 6, TNF, and soluble TNF receptor remained unchanged.44 Fatigue is a common side-effect of interferon therapy, which induces the secretion of interleukins 1, 2, 6, and 8, and TNF-α.53 54 Furthermore, treatment with monoclonal antibody against TNF-α improves health assessment scores, including those of fatigue.55

In summary, whether an increased liberation of cytokines, as a part of the inflammatory reaction in cancer and cancer therapy, is of importance for the development of fatigue, remains controversial.
Psychosocial factors and deconditioning

Cancer-related fatigue is associated with psychosocial factors, such as anxiety and depression,8,9 difficulty sleeping,9,10 full-time employment status,11 and low degrees of physical functioning.1 However, whether it is a cause or an effect of these factors is unknown. Fatigue is also linked to high amounts of other unmanaged symptoms—especially pain.72

Fatigue is inversely associated with activity level and with functional capacity. Sedentary patients with breast cancer who have a reduced exercise tolerance report higher degrees of fatigue during cancer treatment than more active, physically fit patients.12,13,14 Despite this, results from a 1997 survey revealed that when patients reported fatigue to health-care professionals, the frequent recommendation was additional rest and decreased activity.1 Whether a survey done today would result in similar findings, is unknown. However, a consistent decrease in the amount of daily activity over the often lengthy period of cancer treatment could eventually lead to a reduced tolerance for normal activity and, hence, high levels of fatigue.15

Assessment

Decisions about management of cancer-related fatigue are based on assessment of the degree of the problem in the individual patient.16 If interventions are implemented, measures need to be available to assess whether or not they are effective.17 The aims of clinical assessment of fatigue and investigation of fatigue in research are different, but both approaches need methods that are sensitive to changes in levels of fatigue.18 Validated multidimensional methods provide a sophisticated way of assessing fatigue, but they are difficult to use in clinical practice because of time limitations and the burden on the patient, among other factors. Researchers need measures that maximise both variance and precision.19 Furthermore, an observer cannot directly measure fatigue; it can only be assessed by self-report.18

Diagnostic methods

Fatigue is a symptom affected by multiple biological and psychosocial factors.20 When assessing cancer-related fatigue, the health-care provider, therefore, needs to include both subjective and objective data. Portenoy and Irri21 suggest the routine use of three questions to help assess the severity of fatigue and its effect over time: 1) are you experiencing any fatigue? 2) If so, how severe has it been, on average, during the past week? (If fatigue is present a simple 0–10 rating scale can be used—ie, 0–3 is mild fatigue, 4–6 moderate, and 7–10 severe.)22,23 and 3) how does fatigue interfere with your ability to function?

These three questions give the health-care provider some knowledge of the patient’s status. Moreover, this information can indicate whether there is a need for further investigation, and serves as a baseline for future follow-up. The 0–10 rating scale, however, provides only a unidimensional assessment of the multidimensional notion of fatigue. Winningham and colleagues24 suggest that information on the temporal pattern, the exacerbating and relieving factors, the effect of fatigue on day-to-day activities, the meaning of fatigue to the individual, and the cultural factors that affect expression of feelings of fatigue should also be obtained. A health diary, kept by the patient, can be used to assess fatigue and to ascertain appropriate interventions.25

In the USA, the NCCN proposed in their Fatigue Practice Guidelines an algorithm in which patients are assessed regularly for fatigue, using a brief screening method (figure). Screening for the presence and severity of fatigue should take place at the patient’s initial contact with an oncologist, at appropriate intervals thereafter, and as clinically indicated. If fatigue is reported during screening, it should be quantified for future comparison. When the screening process reveals moderate or severe degrees of cancer-related fatigue, a focused history and a physical examination, including an examination of the patient’s disease and treatment status and an in-depth fatigue...
assessment, is recommended. As part of the assessment, the guidelines identify five common clinical conditions that can cause fatigue and which should be specifically assessed—ie, pain, emotional distress, sleep disturbance, anaemia, and hypothyroidism. If any of these conditions are present, they should be treated as an initial approach to fatigue management. If no primary factor is identified that accounts for the patient’s fatigue, a comprehensive assessment is indicated, including a review of body systems, undiagnosed or unmanaged comorbidities, nutritional status, and the patient’s daily activity patterns and degree of inactivity.

Data from a comprehensive assessment might suggest plausible hypotheses with respect to pathogenesis, which in turn could indicate appropriate strategies for treatment. Other characteristics of fatigue—eg, onset, duration, severity, daily pattern, time course, exacerbating and reducing factors, and distress caused—are also important when trying to decide on a treatment strategy. The NCCN guidelines provide an overall framework for clinical practice, but no outcomes research has been undertaken to ascertain their effectiveness.

Research instrument
Since fatigue is primarily a subjectively experienced symptom, self-report measures are the most commonly described type of instrument for measuring fatigue. According to Piper, at least 18 self-reported instruments have been developed.

Piper and associates submit that they were the first to propose a multidimensional measurement model for fatigue manifestations. That model was strongly affected by what was known about pain manifestations at the time. Fatigue is considered to be a multidimensional construct, but this point is not always reflected in the choice of measurement strategies. Comparison of the methods is hindered by the fact that there has been little standardisation of fatigue measurement between studies. Available self-report methods can basically be divided into so-called one-dimensional or multidimensional approaches. The response formats of these approaches include yes or no, Likert-type scales, and visual analogue scales. Although several instruments have been developed, they generally require further psychometric testing within the cancer population.

The Piper fatigue scale
The Piper fatigue scale, in its revised version, covers four subjective dimensions (cognitive, behavioural, sensory, and affective) and also includes three open questions with respect to cause, other symptoms, and relief measures. The scale contains 22 items scored on a scale of 0 to 10. Standardised $\alpha$ for the total scale is at least 0.89. The length of the Piper fatigue scale might be a burden for patients if used in clinical practice. However, it is probably the most comprehensive and multidimensional method available for use as a research instrument.

The functional assessment of cancer therapy fatigue scale (FACT-F)
The FACT-F consists of the 28 items of the FACT-general, to assess health-related quality of life, and an additional 13 items to assess fatigue. The FACT-F has high internal consistency (overall $\alpha=0.95$; $\alpha$ for fatigue subscale=0.93–0.95). The length of the entire questionnaire could burden fatigued patients, but the fatigue subscale is brief, simple, and easy to use. The questionnaire is designed for patients in treatment, which could be a limitation.

The Schwartz cancer fatigue scale
This scale has 28 items separated into four subscales: physical, emotional, cognitive, and temporal. It has good validity (overall $\alpha=0.96$, $\alpha$ for subscales=0.82–0.93). It is simply worded but long. This scale also exists in a revised version, with six items measuring two dimensions: physical and perceptual. The revised Schwartz cancer fatigue scale has high internal consistency ($\alpha=0.90$).

The multidimensional fatigue inventory (MFI-20)
The MFI-20 covers five areas—general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue—and consists of 20 items. MFI-20 has been used in several studies of cancer patients and has shown good reliability ($\alpha=0.65–0.80$) in patients receiving radiotherapy. However, the instrument needs to be tested in other cancer populations.

The brief fatigue inventory
The brief inventory comprises nine items measured on a ten-point scale that assesses the severity of fatigue and its effects on the patient’s ability in activities of daily living. The inventory has a high internal consistency ($\alpha=0.96$). It is short and easy to use, but has only a single-dimension measure of fatigue.

The cancer linear analogue scale (CLAS)
Also known as the linear analogue scale assessment (LASA), CLAS includes one or a series of symptoms or outcomes related to symptoms—such as quality of life and ability to undertake daily activities. Patients score their perceptions of these symptoms by placing a mark on a 100 mm line to indicate magnitude of the symptom. CLAS/LASA measures are thought to be reliable and valid, and have been used widely in cancer populations. Advantages include low burden to patients, the ability to measure several symptoms concurrently, and ease of clinical use. Disadvantages include unidimensionality and some reported difficulties when elderly patients try to use the scale.

General
When measuring cancer-related fatigue there are several factors that should be considered. Because fatigue fluctuates in severity over time it should be measured as a state rather than as a stable characteristic. Also, potential confounding exists in the measurement of fatigue because of its close association with other factors—eg, depression, muscle weakness, and functional status. Furthermore, instrument reactivity is an essential issue with cancer-related fatigue, because respondent burden can induce the condition. Research designs should include measurement of multiple symptoms simultaneously, in an attempt to define and correlate the constellation of symptoms that can arise with fatigue or could be cofactors in the cause of fatigue. These symptoms generally include fatigue, difficulty in sleeping, pain, and emotional distress, especially depression.

Management
The most effective approach to symptom management is to identify the cause of the distressing symptom and correct it. However, in many patients with cancer, no cause for fatigue can be readily identified, and the approach to management is a general one.
## Panel 1: Effects of exercise on cancer-related fatigue

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample</th>
<th>Design</th>
<th>Type of exercise</th>
<th>Results</th>
<th>Comments</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacVicar and Winningham, 1986&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Breast cancer CT no staging data, n=10; healthy n=6</td>
<td>Quasi-experimental 3-group</td>
<td>Laboratory cycle, ergometer 3 times per week for 10 weeks 60–85% heart rate maximum</td>
<td>↑ Functional capacity ↓ Mood disturbance and fatigue in exercising patients (n=6) and exercising non-patients (n=6) ↑ Mood disturbance in controls (n=4)</td>
<td>Non-random group assignment, small sample size</td>
<td>2</td>
</tr>
<tr>
<td>Mock et al, 1994&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Breast cancer CT, stage 1 and 2, n=14</td>
<td>Experimental 2-group</td>
<td>Home-based walking 4–5 times per week for 30 min plus support group</td>
<td>↑ Walking ability in exercisers ↓ Mood disturbance and fatigue, compared with controls Less fatigue in exercisers</td>
<td>Effects of exercise alone cannot be ascertained, fatigue one-item visual analogue scale, exercise was self-reported, small sample size</td>
<td>2</td>
</tr>
<tr>
<td>Mock et al, 1997&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Breast cancer RT, stage 1 and 2, n=46</td>
<td>RCCT</td>
<td>Home-based walking 4–5 times per week for 30 min, treadmill walking 80% heart rate maximum</td>
<td>↑ Walking ability in exercisers ↓ Fatigue and other symptoms compared with controls ↑ Functional capacity in exercisers. Less fatigue in exercisers by anecdote</td>
<td>Exercise was self-reported</td>
<td>2</td>
</tr>
<tr>
<td>Dimeo et al, 1997&lt;sup&gt;100&lt;/sup&gt;</td>
<td>Mixed haematological malignant disease and solid tumours; Post-PBSCT survivors, n=32</td>
<td>Quasi-experimental</td>
<td>Treadmill walking 80% heart rate maximum</td>
<td>↑ Functional capacity and distance walked in exercisers ↓ Fatigue by anecdote ↓ Fatigue and psychological distress in exercisers</td>
<td>No fatigue measures, small sample size</td>
<td>2</td>
</tr>
<tr>
<td>Dimeo et al, 1998&lt;sup&gt;105&lt;/sup&gt;</td>
<td>Mixed cancer survivors post-PBSCT, n=5</td>
<td>1-group pretest/post-test</td>
<td>Bed cycle ergometer 50% heart rate maximum</td>
<td>No exercise outcomes reported</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Dimeo et al, 1999&lt;sup&gt;102&lt;/sup&gt;</td>
<td>Mixed haematological malignant disease and solid tumours PBSCT, n=59</td>
<td>RCCT</td>
<td>Home-based walking or patient’s choice 3 times per week</td>
<td>↑ Pretest to post-test walking ability ↑ Quality of life and less fatigue in active exercisers vs non-compliers</td>
<td>60% of participants adhered to programme, single group design</td>
<td>3</td>
</tr>
<tr>
<td>Schwartz, 1999&lt;sup&gt;114&lt;/sup&gt; and 2000&lt;sup&gt;114&lt;/sup&gt;</td>
<td>Breast cancer CT, stage 1–3, n=27</td>
<td>1-group pretest/post-test</td>
<td>Home-based walking 4–5 times per week for 30 min</td>
<td>↑ Walking ability in exercisers ↓ Fatigue and other symptoms compared with controls ↑ Pretest to post-test walking ability ↓ Fatigue in active exercisers</td>
<td>Exercise was self-reported, 70% adherence in exercise group 61% of participants adhered to programme, single group design</td>
<td>2</td>
</tr>
<tr>
<td>Schwartz et al, 2001&lt;sup&gt;105&lt;/sup&gt;</td>
<td>Breast cancer CT, stage 1–3, n=111</td>
<td>1-group pretest/post-test</td>
<td>Patient’s choice 3–4 times per week for 15–30 min for 8 weeks</td>
<td>↑ Walking ability in exercisers ↓ Fatigue and other symptoms compared with controls</td>
<td>Exercise was self-reported, 72% adherence in exercise group 100% of participants adhered to exercise, 67% adhered to methylphenidate, small sample size</td>
<td>3</td>
</tr>
</tbody>
</table>

CT=chemotherapy. RT=radiation therapy. PBSCT=peripheral blood stem-cell transplant. RCCT=randomised controlled clinical trial. "1=meta-analyses or systematic review; 2=randomised clinical trial or well-designed multiple group quasi-experimental study; 3=single-group study; 4=consensus that includes clinical judgment; 5=expert opinion." Adapted from Mock V et al. Cancer-related fatigue clinical practice guidelines in oncology, NCCN (version 1.2003). J Nat Comp Cancer Network (in press). Copyright National Comprehensive Cancer Network. To view the most recent and complete version of the guideline, go online to www.nccn.org. Guidelines copyrighted by National Comprehensive Cancer Network. All rights reserved. This panel may not be reproduced in any form for any purpose without the express written permission of the NCCN.
Panel 2: Effects of psychosocial interventions on cancer-related fatigue

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample</th>
<th>Design</th>
<th>Intervention</th>
<th>Results</th>
<th>Comments</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiegel et al, 1981120</td>
<td>Breast cancer stage 4, n=86</td>
<td>RCCT</td>
<td>Support group every week for 1 year</td>
<td>↓ Anxiety, fatigue, confusion, and mood disturbance in experimental group</td>
<td>Fatigue measured by subscale on POMS</td>
<td>2</td>
</tr>
<tr>
<td>Forester et al, 1985118</td>
<td>Mixed cancer treated RT, n=100</td>
<td>RCCT</td>
<td>Individual psychotherapy every week for 10 weeks</td>
<td>↓ Emotional and physical symptoms in experimental group</td>
<td>Fatigue measured by single item on the schedule of affective disorders and schizophrenia</td>
<td>2</td>
</tr>
<tr>
<td>Fawzy et al, 1990118</td>
<td>Melanoma post-surgery, stage 1 and 2, n=66</td>
<td>RCCT</td>
<td>Support group (including education and stress management) every week for 6 weeks</td>
<td>↑ Coping and vigour in experimental group at 6 weeks ↓ Fatigue, depression, and mood disturbance at 6 months’ follow-up</td>
<td>Fatigue measured by POMS</td>
<td>2</td>
</tr>
<tr>
<td>Fawzy, 1995111</td>
<td>Melanoma stage 1 and 2, n=61</td>
<td>RCCT</td>
<td>Individual education and support by registered nurse 3 h total</td>
<td>↓ Fatigue, anxiety, and mood disturbance in experimental group</td>
<td>Fatigue measured by POMS</td>
<td>2</td>
</tr>
<tr>
<td>Gaston-Johansson et al, 2000121</td>
<td>Breast ABMT n=110</td>
<td>RCCT</td>
<td>Comprehensive coping strategy programme</td>
<td>↓ Fatigue and nausea in experimental group</td>
<td>Covariates controlled, fatigue measured by visual analogue scale</td>
<td>2</td>
</tr>
<tr>
<td>Barsevick et al, 2002115</td>
<td>Mixed cancer RT or CT, n=38</td>
<td>RCCT</td>
<td>Energy conservation and activity management pretest/posttest</td>
<td>↑ Coping and vigour in experimental group at 6 weeks ↓ Fatigue, depression, and mood disturbance at 6 months’ follow-up</td>
<td>Fatigue measured by POMS, feasibility of energy conservation and activity management established</td>
<td>3</td>
</tr>
<tr>
<td>Barsevick et al, 2002116</td>
<td>Mixed cancer RT or CT, n=350</td>
<td>RCCT</td>
<td>Energy conservation and activity management</td>
<td>↓ Fatigue in experimental group</td>
<td>Fatigue measured by POMS</td>
<td>2</td>
</tr>
<tr>
<td>Given et al, 2002122</td>
<td>Mixed solid tumours and lymphoma CT, stage 1–4, n=113</td>
<td>RCCT</td>
<td>Tailored behavioral intervention in 10 contacts in 18 weeks</td>
<td>↑ Fatigue and pain ↓ Physical and social functioning in experimental group at 20 weeks</td>
<td>Fatigue measured by the symptom experience scale (measures “present” or “absent” only)</td>
<td>2</td>
</tr>
<tr>
<td>Jacobsen et al, 2002123</td>
<td>Mixed cancer CT n=411</td>
<td>RCCT</td>
<td>Stress management training PSMT or SSMT</td>
<td>↑ Physical functioning, mental health, vitality in SSMT; ↓ costs for SSMT</td>
<td>Fatigue measured as vitality on medical outcomes study short form-36</td>
<td>2</td>
</tr>
</tbody>
</table>

RT=radiation therapy. ABMT=autologous bone marrow or peripheral blood stem cell transplantation. CT=chemotherapy. RCCT=randomised controlled clinical trial. PBSCT=peripheral blood stem cell transplant. PSMT=professionally administered stress-management training. SSMT=self-administered stress-management training. POMS=profile of mood state scale. *1=meta-analyses or systematic review; 2=randomised clinical trial or well-designed multiple group quasi-experimental study; 3=single-group study; 4=consensus that includes clinical judgment; 5=expert opinion.97


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Non-pharmacological interventions

Education

Research has documented the beneficial effects of providing patients with preparatory knowledge, including sensory information, about their disease and treatment. If patients receive valid information about what to expect, they are more likely to develop accurate expectations and are less likely to experience the stress that accompanies unforeseen problems. For example, uninformed patients often interpret fatigue to mean that their cancer treatment is not working or that their disease is progressing. With appropriate educational grounding, patients can prepare for side-effects and adopt management strategies. However, the limited research on educational and preparatory information for patients with cancer has not looked specifically at fatigue as an endpoint, but has shown more positive emotional outcomes and decreased disruption in usual activities.

Exercise

In the management of fatigue, exercise is the intervention with the most supporting evidence of effectiveness. The theory supporting exercise as a treatment for fatigue proposes that the combined toxic effects of cancer treatment and a decreased degree of
physical activity during treatment cause a reduction in the capacity for physical performance. When patients must use greater effort and expend more energy to succeed in daily activities, fatigue levels increase. Exercise training leads to a reduction in the loss or even an increase in functional capacity, leading to reduced effort and decreased fatigue.113 There are 11 published reports by four research teams, to date, of studies testing the effects of exercise on fatigue during active cancer treatment, and two additional reports of exercise programmes after cancer treatment (panel 1).5,6,8,7,47,114 All indicate significantly lower levels of fatigue in individuals who exercised than in controls. Although the results have been consistent across studies, the studies are limited in number, sample sizes of most are small, and there are methodological limitations associated with many. Furthermore, most studies have only included patients with breast cancer.

The types of exercise reported varied, but all were considered aerobic. There were some home-based walking programmes5,6,8,7,47,101–105 and some supervised laboratory treadmill or exercise bicycle formats.9,116–118 The programmes varied in length from 6 weeks for patients undergoing radiation therapy to 6 months for chemotherapy and through extensive peripheral blood stem-cell transplantation. Most of the participants were women with breast cancer, with the exception of three studies of patients with haematological malignant disease treated with peripheral blood stem-cell transplantation.116–118 Fatigue was measured by various self-report methods, whereas changes in exercise tolerance and functional capacity were measured by symptom-limited exercise tests or a timed walk test. The study designs include single-group pretest and post-test, quasi-experimental, and randomised clinical trials.

In addition to the individual studies reported in panel 1, two reviews of exercise studies in patients with cancer have also concluded that exercise reduces fatigue and improves quality of life.117,118 Results of a pilot study of increased activity in nine patients with advanced cancer also showed reductions in fatigue.119 Only one small study (n=5) of the investigations of effects of exercise on fatigue involved institution of an exercise programme for individuals complaining of high levels of fatigue.120 All of the others were studies of exercise programmes offered to a group of patients at a set point in their therapy (before or after cancer treatment) irrespective of their level of fatigue. There is limited information about the effectiveness and acceptability of an exercise programme designed for patients who already have high levels of fatigue.

Rest and sleep

Patients with fatigue are often advised by health-care professionals to get additional rest and sleep.7 The relation between sleep disturbance and fatigue has been inadequately investigated.111 Patients with cancer report significant disruptions in sleep, and the essential issue may be sleep quality rather than quantity.39 Results of two studies, which used actigraphy to measure activity and sleep, have shown that cancer patients spend more time resting and sleeping than healthy individuals, but that the pattern of sleep is often severely disrupted with awakening almost every hour.112,113 Patients who try additional rest and sleep to manage fatigue do not report it to be particularly effective.113 The research being done to test rest or sleep to manage fatigue is in preliminary stages, and only one abstract of a pilot project has been published.114

Energy conservation

Energy conservation is a frequent treatment recommendation for cancer-related fatigue. Although research is limited, results of a pilot study have been published,115 and a multicentre randomised clinical trial is in progress.116 Decreasing activity to save energy could contribute to deconditioning and decreased activity tolerance. Nevertheless, using limited energy to do highly valued activities instead of mundane tasks that can be delegated could increase personal satisfaction and quality of life as well as manage fatigue.

Stress reduction

Studies testing interventions to reduce stress and increase psychosocial support have also shown reductions in fatigue, usually as a component of mood state.117–122 Because these interventions did not have fatigue as a primary endpoint, fatigue measures are often limited to a subscale on an instrument to measure emotional distress, and the interventions generally did not attempt to elucidate a mediating mechanism of fatigue. Cancer-related fatigue could be a response to stress, or the emotional state of a patient could affect the way he or she perceives and reports fatigue. Although a strong correlation exists between emotional distress and fatigue,61,73,119 the precise relation is not clearly understood.

The specific interventions tested have included support groups, counselling, and a comprehensive coping strategy (panel 2).77,115–123 In the studies of support groups, the experimental groups have shown less overall mood disturbance, less depression, less fatigue, and greater vigour than control groups on the profile of mood states scale.118,120 A comprehensive coping strategy programme was tested in a randomised controlled clinical trial to see whether it could reduce pain, fatigue, nausea, and psychological distress in 110 breast-cancer patients undergoing autologous bone marrow transplantation.131 The coping strategy programme included components of preparatory information, cognitive restructuring, and relaxation with guided imagery practiced daily from baseline until 7 days after transplantation. The programme significantly reduced fatigue combined with nausea 7 days after transplantation, but there were no significant differences in the two groups with respect to fatigue alone.

A model of cognitive or attentional fatigue in patients with cancer has been described by Cimprich.124 The theory is that during stressful situations, such as occurs during the increased demands of life-threatening illness and treatment, directed attention could become impaired with a resulting loss of concentration. Cimprich developed and tested an attention-restoring intervention in post-surgical patients with breast cancer, involving restorative experiences with the natural environment. Participants in the experimental group showed enhanced attentional capacity on various neurocognitive tests and returned to work earlier than controls. The research in this area is preliminary and needs further development. Also, the relation between attentional fatigue and cancer-related fatigue is unclear, since no measures of self-reported fatigue levels were used in the studies.

A randomised clinical trial has been done to test a supportive care management intervention to manage pain and fatigue during chemotherapy in a sample of 113 patients with mixed diagnoses, stages 1–4.125 The intervention was tailored to the patients’ problems and included
teaching, counselling and support, coordination, and communication. Pain and fatigue, as well as total symptoms, were reduced in the experimental group, and both physical and social role function were significantly higher than in controls.

Pharmaceutical therapy
Three large community-based non-randomised studies126–128 and two double-blind randomised clinical trials119,120 have shown a clinical benefit of eptoplatin alfa treatment on cancer-related anaemia and fatigue. In these studies, erythropoietin alfa reduced the need for transfusions, decreased fatigue levels, and improved quality of life in patients receiving chemotherapy. Published guidelines support this conclusion.118 The new erythropoietic agent, darbepoetin alfa, has shown similar outcomes with less frequent dosing.119,120

Few controlled studies have been done to investigate other pharmacological therapies for cancer-related fatigue or therapy-related fatigue. In search of an active agent to combat cancer-related cachexia, megestrol acetate has been investigated in several studies and been found to alleviate anorexia and improve weight.131,132 In another study,133 this drug reduced fatigue to some degree in patients with advanced cancer. Accordingly, prednisone was more effective than flutamide in improving quality of life, including degree of fatigue, in patients with prostatic cancer.130 Psychostimulants have been effective in reducing fatigue related to HIV-1 infection134 and in multiple sclerosis,135 but there are limited data with respect to efficacy in cancer-related fatigue.

In a small randomised study,136 amifostine administered with paclitaxel to women with breast cancer did not affect therapy-induced fatigue.1 Methylphenidate has been used effectively in the palliative care setting to ameliorate opioid-induced somnolence and to improve cognitive function; however, fatigue was not reported.137 A pilot study of 12 patients with melanoma who were receiving interferon compared methylphenidate plus exercise to exercise alone to fatigue levels of historical controls. Fatigue was lower for the methylphenidate plus exercise group than for the comparison groups.138

Conclusion
Although fatigue is the most prevalent symptom reported by cancer patients, the assessment and management of this distressing side-effect of cancer and cancer treatment has been limited. This paucity of work is related to many factors, including a lack of understanding of the mechanisms responsible for cancer-related disease, a lack of awareness by cancer-care providers of the importance of the problem, and a lack of evidence-based interventions to manage the condition.139

Treatment of anaemia improves a patient’s fatigue levels and quality of life.130,132–137 However, when a patient is not anaemic, the most common interventions for fatigue are behavioural ones, with exercise and psychosocial interventions as the most effective. Research into other management methods, such as energy conservation and sleep, is continuing.

Several important gaps exist in our knowledge of how to manage cancer-related fatigue, and these are reflected in our recommendations for future research (panel 3).

Theories that underlie interventions being tested have not been well explained, and thus our understanding of the mediating mechanisms of fatigue is insufficient. Study designs have been limited by lack of control groups, small sample sizes, and other threats to validity and reliability. Furthermore, little research has been undertaken in patients with advanced disease or those who are elderly, have low socioeconomic status, or are ethnically diverse. These patients present obvious challenges as research participants, since they are often more debilitated and have many comorbidities and life demands that make their involvement in research difficult, and that often confound findings. Additionally, ethnic and cultural diversity is often limited in research studies because valid and reliable instruments are not available in a variety of languages.

Nevertheless, the science related to cancer-related fatigue is developing rapidly, research-based clinical practice guidelines for fatigue management are now available,131 and awareness by health-care professionals of the importance of this disruptive symptom is greater than ever.

Conflict of interest statement
None declared.

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