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Review

Fatigue in Patients with Cancer

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This paper reviews current knowledge regarding cancer-related fatigue assessment, prevalence, mechanisms and management. Most quality of life questionnaires contain at least some items pertaining to fatigue and a number of more specific self-assessment tools have now also been developed. As a result, there is a growing body of literature which documents the extent and severity of fatigue in cancer populations. Unfortunately most of these studies are uncontrolled and do not, therefore, provide an accurate estimate of the prevalence or severity of cancer fatigue relative to that found in the general population. Data from controlled studies are limited and the results are conflicting. Cross-sectional studies suggest that fatigue is the result of a combination of physical and psychological causes. Although no one treatment is proven to alleviate cancer-related fatigue a number of strategies show therapeutic promise. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

FATIGUE IS a difficult symptom to define, but broadly speaking can be understood as a subjective sensation of weakness, lack of energy or becoming easily tired. Although feelings of fatigue are often associated with demonstrable decrements in performance, the symptom itself cannot be directly measured by an observer and can only be assessed by self-report. Fatigue is a common complaint in the general population and is also a symptom of both physical and mental illnesses. In cancer patients, fatigue has been shown to have a considerable impact on self-care abilities [1–5] and quality of life [6]. In recent years, it has been demonstrated that, with attention to detail and good clinical practice, cancer pain can be controlled in the vast majority of patients [7]. Fatigue now probably represents the most common unrelieved symptom of cancer [8–10]. This paper reviews current knowledge regarding fatigue assessment, prevalence, mechanisms and management.

WHAT IS MEANT BY FATIGUE?

There are at least two distinct meanings of the term fatigue.

- It may be a *subjective* state characterised by feelings of weariness and a perception of decreased capacity for physical or mental work. Qualitative studies [11, 12] have suggested that patients with cancer experience at least three distinct dimensions to the feeling of fatigue; physical sensations (e.g. feeling unable to perform tasks, weakness, an unusual feeling of tiredness), affective sensations (decreased motivation, low mood, no energy) and cognitive sensations (lack of concentration, difficulty thinking clearly).
- It may be defined as an *objective* decrement in physical or mental performance, with repeated or prolonged activity.

These two aspects of fatigue are not simply related. One may feel fatigued without any objective decrement in performance and vice versa. This review is primarily concerned with subjective fatigue.

HOW IS FATIGUE MEASURED?

Fatigue is included as a subscale in several cancer-specific quality of life measures, including the European Organisation for Research and Treatment of Cancer questionnaire (EORTC QLQ c-30) [13] and the Rotterdam Symptom Checklist (RSCL) [14]. The EORTC QLQ c-30 contains a three-item fatigue subscale (During the past week: 'Did you need to rest?' 'Have you felt weak?' and 'Were you tired?') each item of which can be answered on a four point scale ('Not at all', 'A little', 'Quite a bit', 'Very much'). Although widely used, these measures are not suitable for in-depth studies of fatigue, because they only contain a few items with

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a limited number of possible responses. As a consequence, large numbers of patients are required in order to detect quite modest changes in fatigue level.

Over the years, a number of more comprehensive self-report fatigue scales have been developed. The available instruments broadly fall into two main categories depending on whether they simply measure fatigue intensity (unidimensional scales) or they attempt to gauge the quality of the symptom as well as its severity (multidimensional instruments). The multidimensional fatigue scales which have been produced assess fatigue in anything from two (the 'Chalder' fatigue scale) to five dimensions (the MFI-20). Examples of commonly used scales are given in Tables 1 and 2.

WHAT IS THE PREVALENCE OF FATIGUE?

The prevalence of fatigue in cancer patients receiving chemotherapy has been reported to range between 75 and 96% [5, 26–29]. For patients receiving radiotherapy, the reported range is 75–100% [2, 30–33] and for those with advanced cancer, it is 33–89% [34–41]. However, one of the difficulties with interpreting these figures is the recognition that fatigue is also a common complaint in the community. Cox and colleagues [42] reported that 20% of men and 30% of women 'always feel tired' and Shepherd and associates [43] reported that 13% of men and 23% of women 'often get spells of complete exhaustion or fatigue'. It is currently unclear how much of the fatigue experienced by cancer patients is in excess of that found in the general population.

Indirect evidence for excessive fatigue in cancer patients can be derived from studies using questionnaires which have also been validated in healthy populations. King [44] reviewed 14 published studies which have used the EORTC QLQ c-30. Scores on the fatigue subscale of this instrument range between 0 (no fatigue) and 100 (maximum fatigue). In

Table 1. *Examples of unidimensional fatigue scales*

	Description of scale	Comments
Rhoten Fatigue Scale [15]	A visual analogue scale combined with a 10-point rating scale.	Very simple to administer. Lack of reliability and validity data, but has been used in a number of fatigue studies.
Pearson and Byars Fatigue Feelings Checklist [16]	Consists of 10 items which subjects are asked to rate on a 10-point adjectival scale ranging from 'extremely peppy' to 'extremely tired'.	Developed to assess fatigue in airmen who were asked to do repetitive tasks. The scale was developed in the 1950s by American researchers and much of the vocabulary is unsuitable for a modern British population. It exists in two equivalent forms with a high intercorrelation. It has been shown to discriminate between fatigued airmen and controls, but there is a lack of validity data in medically sick populations.
Fatigue Severity Scale [17]	Consists of 9 items with which subjects are asked to indicate their degree of agreement on a 7-point scale e.g. Fatigue is among my three most disabling symptoms.	Relatively simple and quick to complete. It has been validated in a limited number of patients with MS and SLE and was found to be able to distinguish well between patients and controls and to be sensitive to changes in fatigue over time.

MS, multiple sclerosis; SLE, systemic lupus erythematosis.

Table 2. *Examples of multidimensional fatigue scales*

	Description of scale	Comments
'Chalder' Fatigue Scale [18]	An 11 item scale addressing physical and mental fatigue. Each item is scored on a 4-point scale, e.g. Have you felt weak? Have you had problems thinking clearly?	The shortest of the multidimensional instruments. This scale (or similar versions) has been used in large community studies of fatigue and chronic fatigue syndrome [19–21]. It was validated against the fatigue item in the Clinical Interview Schedule and found to have a sensitivity of 75.5% and a specificity of 74.5%.
Fatigue Symptom Checklist [22]	Consists of 30 items forming three subscales: physical fatigue, mental fatigue and malaise.	It was developed by the Japanese Industrial Research Committee on Fatigue and was designed to assess fatigue in the workplace. It has been adapted for use in medical populations and used to study fatigue levels in cancer patients undergoing radiotherapy [23]. The cross-cultural validity of the scale has not been explored.
Piper Fatigue Scale [24]	Consists of 76 visual analogue scales assessing fatigue in four dimensions: temporal, intensity, affective and sensory.	It is a long questionnaire designed for research purposes rather than clinical use. It has demonstrated good internal consistency (Cronbach's alpha = 0.85), but only moderate convergent validity with other fatigue scales.
Multidimensional Fatigue Inventory [25]	A 20 item questionnaire made up of five subscales: general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue. Each item is answered on a 5-point scale.	This was specifically designed for use in cancer patients. It has good internal consistency (Cronbach's alpha = 0.8) and construct validity. However, it appears that with the exception of mental fatigue, all of the subscales behave more or less similarly—suggesting that the distinction between these dimensions may not be very relevant.

these studies, fatigue appeared to be more severe in those patients who were on treatment or who had worse performance status or more extensive disease. The mean fatigue score for patients on treatment was approximately 50. For comparison, the mean fatigue score using the same measure in a sample of 608 Danish women was 26 [45].

Direct evidence for increased fatigue levels in cancer patients can be obtained from studies which have included a healthy control group. Bruera and colleagues have reported three studies of asthenia (defined by the authors as physical or mental fatigue/weakness) involving both patients with advanced breast cancer (i.e. locally recurrent or metastatic disease) and healthy controls. Excessive asthenia was defined in relation to either the 5th or the 10th centile of the control group. The proportion of patients defined as having significant asthenia was 20% [46], 72% [9] and 41% [47] in the three studies. Although other controlled studies have also demonstrated increased fatigue levels in cancer patients [48, 49], this has not always been the case. Smets and associates [25] failed to show consistent differences in general fatigue between a heterogeneous group of cancer patients receiving radiotherapy and soldiers in training, junior physicians, psychology students or medical students, and other investigators have failed to find significant differences in fatigue between cancer patients and healthy volunteers [50, 51]. Overall, however, the evidence supports the clinical impression that fatigue is more common in cancer patients and is a cause of considerable distress [26].

WHAT ARE THE CAUSES OF CANCER-RELATED FATIGUE?

Fatigue is a common symptom of many physical illnesses and is also commonly associated with affective disorders. The experience and expression of fatigue is also likely to be affected by social and existential factors, such as whether one feels supported socially and whether one feels a sense of purpose or meaning in life. All of these factors may contribute to the experience of fatigue in cancer patients, although the relative contribution of each factor in an individual patient may well vary over the course of the illness. Much of the research to date has focused on correlating the severity of fatigue with the more easily assessable physical factors.

Physical correlates of fatigue

Cachexia and weight loss. It is only recently that clinicians have begun to think of fatigue as reflecting a different symptom complex to cachexia [52]. This is because both symptoms occur commonly in patients with advanced cancer. Cachexia results in loss of muscle bulk and this in turn leads to weakness. However, neither Bruera and colleagues [47] nor Morant and associates [53] were able to find a correlation between subjective fatigue and nutritional status in patients with advanced cancer. Both of these studies had limitations. Bruera and colleagues did not use a validated tool to measure fatigue and most of their patients were on chemotherapy, which may have resulted in fatigue in the absence of cachexia. The study of Morant and associates was small and defined fatigue with reference to a control population who were on average 25 years younger than the patients.

Muscle abnormalities. Loss of bulk is not the only muscle abnormality that has been observed in patients with cancer. Histology of muscle in cancer patients has demonstrated selective atrophy of type II fibres [54]. Bruera and colleagues [55] have investigated muscle electrophysiology in patients with advanced breast cancer. They observed abnormal electrophysiology that was not associated with abnormal nutritional status or decreased muscle mass. Voluntary muscle function was not impaired. A preliminary report of this study [46] demonstrated a relationship between the electrophysiological abnormalities and subjective feelings of fatigue. Unfortunately, the final report made no mention of this association.

Biochemical and haematological abnormalities. It is known that various biochemical abnormalities can result in weakness (e.g. hypokalaemia, hypophosphataemia, hypocalcaemia and hypomagnesaemia). The prevalence of these abnormalities in fatigued patients with cancer is not known. One might expect that anaemia would be a common cause of fatigue in these patients, but evidence to support this is limited. Bruera and colleagues [47] failed to find a significant correlation in 64 patients with advanced breast cancer, whereas Morant [50] found a weak ($r = -0.187$), but statistically significant association in a mixed group of cancer patients. Gleeson and Spencer [56] undertook a study on the use of blood transfusion in palliative care patients and found a significant, but small, improvement in weakness in those who were transfused.

Endocrine abnormalities. Although hypothyroidism causes fatigue in otherwise healthy individuals, no association between thyroid function and cancer-related fatigue was found in Morant's cross-sectional study [50]. There have been a limited number of studies looking at testosterone levels in patients with advanced cancer [57–59]. Although low testosterone levels appear to be common in such patients [60] and are associated with worse nutritional status, no investigator has attempted to correlate this with fatigue. The role of other potential endocrine causes of fatigue in cancer patients has not been properly evaluated.

Cytokines. There has been little research into the relationship between cytokines and cancer-related fatigue. Greenberg and associates [61] assessed fatigue in 15 patients undergoing radiotherapy for prostate carcinoma. They found that fatigue levels rose throughout treatment and that the rise in fatigue was associated with an increase in serum interleukin-1 (IL-1). This is in contrast to Morant [50] who found no such relationship between fatigue and serum tumour necrosis factor (TNF), IL-1, IL-2, IL-6, soluble IL-1 or IL-2 receptor levels.

Psychological correlates of fatigue

Depression. Fatigue is common in depression, and both fatigue and depression are common in cancer patients. Derogatis and colleagues [62] reported that 6% of cancer patients had a diagnosis of major depression and 32% of patients had an adjustment disorder with depressed mood. Bruera and associates [47], Morant [50] and Smets and colleagues [63] have all found that depression correlates significantly with the degree of fatigue in cancer patients. The relationship between these two constructs is clearly complex. Fatigue may be a cause or a result of depression, or the association between the two may be partly due to a lack of specificity in the self-report instruments that have been used. More research is needed to clarify this complex issue.

Personality type. Individuals with certain personality types may be more susceptible to the development of chronic fatigue,

or more likely to report such symptoms. Research into chronic fatigue syndrome has suggested that the traits of emotionality [64], neuroticism [64, 65] and perfectionism [65] are particularly associated with increased complaints of fatigue. It is reasonable to suppose that similar psychological mechanisms may be at work in the development or expression of cancer-related fatigue, but this issue has not yet been adequately addressed.

Stress. One commonly held view for the origin of fatigue is that it is due to prolonged stress [66]. Initially, a stressed individual responds by becoming more alert and ready for 'fight or flight'. With prolonged stress, it has been proposed that the individual adopts a protective mechanism of energy conservation that leads to feelings of fatigue and results in reduced activity. According to this model, the fatigue of cancer patients would be partly explained by the multiple stresses (physical, mental, environmental) that they experience. In support of this view, there is evidence that fatigue levels are positively correlated with increased levels of pain [67], dyspnoea [68], nausea [69] and emotional upset [26, 32, 69] which could all be considered as potential 'stressors'. Although, it is possible that this association is simply due to these symptoms all being more common in patients with advanced disease.

HOW CAN FATIGUE BE MANAGED?

One of the reasons for the previous lack of interest in fatigue as a topic for research has been the lack of any effective interventions to improve it. Fatigue has usually been thought of as an unavoidable accompaniment of cancer and its treatment, and patients have been advised that it is just something that they have to learn to live with. It is unusual to find a specific and easily correctable cause for fatigue, but when one is found it should be treated. Examples would include thyroxine replacement therapy in hypothyroidism or blood transfusion in a symptomatic anaemic patient. More commonly, no cause for the fatigue is identified other than the fact that the patient has cancer or has recently had anticancer therapy. In these circumstances there are a number of nonspecific therapeutic options available.

Non-drug treatments

Exercise. In healthy individuals, exercise is often said to be effective in reducing fatigue. Recent evidence also suggests that exercise is beneficial in patients with chronic fatigue syndrome [70]. Mock and colleagues [71] have reported the results of a randomised controlled study into the effects of exercise in patients with early breast cancer (stage I or II) undergoing postoperative radiotherapy. They demonstrated a significant reduction in fatigue in the patients ($n = 22$) who exercised (a brisk 30 min walk five times per week) when compared with a group of patients ($n = 24$) who received usual care. The subjects studied were all relatively fit to start with and it is not clear that these results would be applicable to the majority of cancer patients in whom fatigue is a problem. These results do, however, support previous work which has also suggested that exercise may be beneficial in patients with early stage breast cancer [72–75].

Rest. In contrast to this, there are some indications that patients themselves find that rest, rather than exercise is effective in relieving their fatigue. Both Dodd [76] and Nail and associates [27] reported that patients receiving radiotherapy or chemotherapy found that taking naps and decreasing activity were moderately effective in reducing their fatigue. Although anecdotally helpful, excessive rest could theoretically aggravate the problem by leading to deconditioning and further loss of functional capacity.

Information. Many patients seem to be unprepared for fatigue as a side-effect of anticancer treatment. Love and colleagues [28] reported that only 8% of patients about to start chemotherapy expected tiredness to be a problem, but that 86% of them subsequently experienced it. There have been no studies which have specifically investigated the role of providing better patient information on reducing treatment-related fatigue. However, there is tangential evidence of a favourable outcome from studies which have looked at the more general benefits of patient education. Rainey [77] compared a mixed group of 30 patients undergoing radiotherapy who received standard care and 30 patients who received more extensive education (in the form of a 12 min audiovisual programme). He reported that the subjects exposed to more pretreatment information experienced less emotional distress at the end of their therapy. A similar study by Johnson and associates [78] randomised 84 patients with prostate cancer to receive either standard care or more detailed preradiotherapy information (in the form of four audiotaped messages). They reported that the group receiving more in-depth information experienced less disruption to their usual activities throughout radiotherapy and for up to 1 month afterwards decreased disruption of normal activities.

Psychological interventions. As psychological distress is consistently correlated with fatigue, it is possible that measures which reduce the former may also reduce the latter. Some studies of psychological interventions in cancer patients have included a measure of fatigue even though this was not the central issue under study. Spiegel and colleagues [79] studied the effects of weekly group support meetings for patients with metastatic breast cancer in the context of a randomised controlled trial. Because of the nature of the patient population, there was a fairly high attrition rate to the study (of 86 patients randomised only 30 were able to complete all four assessments). They found that after 1 year of regular meetings, the intervention group were significantly less fatigued than the control group. Forester and associates [80] investigated the effect of weekly individual psychotherapy sessions on patients undergoing a 6 week course of radiotherapy. They conducted a randomised controlled trial involving 100 patients with a variety of different cancers. After 10 weeks, the patients receiving psychotherapy were significantly less fatigued than the control subjects. Fawzy and colleagues [81] randomised 66 postsurgical patients with malignant melanoma to receive either a 6 week structured psychiatric group support intervention or standard care. Immediately following the therapy, there was a significant difference in vigor levels between the intervention group and controls and a non-significant trend towards decreased fatigue. By 6 months after the treatment, the reduction in fatigue levels had also become significant.

Taken together, these papers suggest that psychotherapeutic approaches can reduce fatigue in cancer patients given sufficient time. This is certainly a therapeutic area which deserves more attention. Further work is needed to determine which groups of patients are most likely to benefit from specific interventions.

Behavioural interventions. Cimprich [82] studied the effect of an intervention to restore attention in a group of

patients with early breast cancer (stage I or II) after surgery. In this small pilot study, 32 patients were randomised to either receive the experimental intervention or usual care. The intervention consisted of undertaking some simple recreational activities for 20–30 min, three times/week. The attentional capacity of these patients was compared with a similar group of patients who were given no such instructions. Over the 90 day study period, there was a significant improvement in measures of attention in the study group. Since many patients express their fatigue in terms of mental slowness and difficulty concentrating, this is a potentially useful intervention which merits further evaluation.

Pharmacological treatments

Corticosteroids. Corticosteroids are often prescribed for their beneficial effects on appetite and general mood, but there is little direct evidence to support their use in the management of fatigue. Moertal and colleagues [83] found a non-significant trend towards improved subjective 'strength' in advanced cancer patients treated with dexamethasone as part of a double blind randomised controlled trial. Bruera and associates [84] found an increase in 'activity level' in 40 palliative care patients after 2 weeks' treatment with methylprednisolone which became non-significant after 4 weeks. ECOG performance status was unaltered in this study and subjective fatigue was not assessed. Finally, Rombustelli Delta Cuna and colleagues [85] conducted a double blind placebo controlled trial of methylprednisolone in 403 patients with advanced cancer. Although they reported improved quality of life over the 8 week period, there was no improvement in self-reported 'weakness'. It should be noted that none of these studies was designed with fatigue as a primary endpoint and so the role of corticosteroids is still open to debate.

Progestational steroids. A number of studies have demonstrated that progestational steroids can increase appetite in cancer patients. Bruera and colleagues [86] incidentally reported an increase in self-reported energy level in patients with advanced non-hormone-dependent cancers treated with megestrol acetate, whereas Downer and associates [87] found no such improvement in patients treated with medroxyprogesterone acetate. Although both studies were double blind randomised and placebo controlled, in neither one was fatigue a primary endpoint, nor was a validated fatigue assessment instrument used.

Anabolic steroids. Chlebowski and colleagues [88] investigated the effect of nandrolone decanoate in patients with advanced non-small cell lung cancer. 37 patients were randomised to receive either nandrolone decanoate or not in an unblinded manner. Median weight loss and the proportion of patients experiencing weight loss were both reduced in the group receiving the anabolic steroid. However, neither difference reached statistical significance. They concluded that further prospective studies were required which used pretreatment testosterone levels as a guide to indicate which patients should receive additional androgen. It would clearly be of interest to determine the effect of androgens on subjective fatigue in any further studies of this treatment.

Psychostimulants. Amphetamines have been suggested for use in cancer patients complaining of excessive drowsiness, especially when this is secondary to opioid analgaesics. One small randomised placebo controlled study in this population has reported that methylphenidate had a positive effect on self-reported activity levels [89]. As yet, the role of these drugs in the management of cancer-related fatigue has not been adequately investigated.

CONCLUSIONS

There is growing interest in the mechanisms and management of cancer-related fatigue. Previous studies have often been hampered by the use of poorly validated assessment methods or a lack of control groups. Since the prevalence of fatigue is high amongst cancer patients, any trial which has quality of life as an endpoint should include an assessment of this symptom. For many purposes, a general quality of life instrument with a fatigue subscale (e.g. the EORTC QLQ c-30) will suffice. In studies where subjective fatigue is of primary interest, then a more detailed assessment instrument should be used. The MFI-20, although still under development, does have the benefits of being multidimensional, specifically designed for cancer patients and relatively short. However, current evidence does not yet allow a firm recommendation about which questionnaire to employ in any given circumstance.

Many causes for cancer-related fatigue have been proposed and it is likely that the symptom is multifactorial in origin. Given the consistent association between fatigue and psychological morbidity that has been found in cross-sectional studies, it is important that future studies of fatigue should also include an assessment of psychological distress. In particular, the nature of the association between depression and fatigue needs to be explored further. This could probably best be achieved by designing longitudinal studies (either interventional or observational) to determine whether fatigue and depression change in tandem or independently.

A number of different therapeutic interventions have been suggested for fatigue, but very few have undergone adequate evaluation. The provision of information about side-effects to patients who are about to undergo cancer treatment and increased psychological support are both promising non-pharmacological approaches. Randomised controlled trials with fatigue as a specific endpoint would help to clarify their role in fatigue management. In patients with good performance status, exercise may have a number of beneficial effects, including reductions in fatigue. The role of pharmacotherapy is less clear. Randomised controlled trials need to be undertaken in order to determine the effectiveness of commonly used drugs such as corticosteroids.

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