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Cancer-related fatigue

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ABSTRACT

Fatigue is a common symptom in patients with cancer and in disease-free survivors. It has a significant impact on the quality of life. Although subjective fatigue is often related to objective changes in physical functioning or impaired performance status, the two phenomena are not synonymous and need to be distinguished. A number of robust and reliable assessment instruments to measure fatigue severity are now available and criteria for cancer-related fatigue syndrome have been proposed. The underlying mechanisms and pathophysiology of cancer-related fatigue are unclear. Management strategies include the use of psycho-educational interventions, exercise programmes and pharmacological treatments. The best evidence for the effectiveness of drug treatments is for the haematopoietic agents in anaemic patients undergoing chemotherapy and for methylphenidate in an on-treatment population.

1. Introduction

Cancer-related fatigue (CRF) is a subjective sensation that is disproportional to the widely recognised feeling of being tired. There is no consensus as to what CRF is and its use in a clinical setting is often colloquial rather than specific.[1] However, it is accepted as a separate entity from the tiredness experienced by the general population. It is characterised by being pervasive and not relieved by rest.[2] CRF can occur at the time of diagnosis and becomes increasingly prevalent with advancing disease.[3,4] It is a side-effect of surgery, chemotherapy and radiotherapy.[5–7] CRF can also affect disease-free survivors.[8]

2. What is cancer-related fatigue?

There is some confusion in the literature regarding the terminology of fatigue. Unfortunately, the same term can be used to describe both an objective physical or mental decrement in performance and a subjective mental state. Both types of fatigue are usually found to a greater or lesser extent in the same individual. However, there is no direct correspondence between the two phenomena. It is quite possible to feel extremely subjectively fatigued but to perform relatively normally on objective tests of physical or mental functioning. It is also possible to have poor physical functioning and not to complain of fatigue at all. The focus of this review is on the symptom of subjective fatigue rather than on physical or mental performance *per se*.

A recent position paper by the European Association of Palliative Care (EAPC) defined fatigue as 'a subjective feeling of tiredness, weakness or lack of energy'.[9] This definition was chosen in order to mirror closely the wording of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQc30), which contains a three-item fatigue sub-scale addressing the symptoms of tiredness, weakness and lack of energy.[10] This working definition of fatigue has the advantage of being simple to understand and easy to remember. The EORTC QLQc30 has also been translated reliably into more than 50 different languages facilitating its use in cross-cultural research projects.

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3. How can cancer-related fatigue be measured?

As a subjective state the most appropriate way to measure fatigue is to use self-report measures. At the simplest level fatigue can be measured by using a single item or a single visual analogue scale, either alone or as part of a broader quality of life assessment tool.[11–13] A single-item, 11-point, numerical rating scale has been advocated as a screening tool for CRF by the National Comprehensive Cancer Network (NCCN).[14] The NCCN guidelines recommend that patients with a score of 0–3 should be considered to have 'none to mild' fatigue and that patients with scores of 4–6 or 7–10 should be considered to have 'moderate' to 'severe' fatigue, respectively. As a quick and easy method to identify patients who may benefit from intervention the numerical rating scale has a lot to commend it. However, single item scales are limited in the extent to which they can capture the subtleties of a complex subjective state like fatigue and most patients who have moderate to severe fatigue should also complete a more comprehensive self-assessment instrument.

A variety of such instruments exist.[15–26] The simplest such questionnaires are 'uni-dimensional' and simply measure the degree or severity of fatigue. A good example of such a scale is the Functional Assessment of Cancer Therapy – Fatigue scale.[17] This is a 13-item free-standing scale which forms part of the 20-item FACT-Anaemia scale. Both scales are part of the modular FACIT (Functional Assessment of Chronic Illness Therapy) quality of life portfolio.[27] The FACT-F has been widely used in CRF studies and is able to detect clinically meaningful differences in fatigue scores in response to treatment.[28–35] Population norms for the FACT-F are also available, facilitating the interpretation of fatigue levels in patient populations.[2,36] One of the limitations of uni-dimensional scales is that the phenomenon of fatigue itself is usually perceived as a multi-dimensional experience.[37] At least two dimensions to the subjective experience of fatigue have been described. Symptoms that might be included in a 'mental fatigue' domain include difficulties with cognition, concentration and speed of mental processes. Symptoms that might be included in a 'physical fatigue' domain include exhaustion, weakness and tiredness. One of the most widely used multi-dimensional scales is the Fatigue Questionnaire (FQ).[15] This 11-item scale (consisting of 7-items on physical fatigue and 4-items on mental fatigue) was originally designed for epidemiological studies in the general population and in patients with Chronic Fatigue Syndrome. It has subsequently been used in a number of studies involving patients with cancer.[33,38–42] The FQ has good psychometric properties and has been shown to be responsive to changes in fatigue levels.[15,41–44] Population norms are also available.[45,46]

One of the problems with conceptualising fatigue as a symptom is that feelings of fatigue are very common in the general population.[44–47] This means that care is required with interpreting fatigue levels in patient groups unless comparison is made with the 'background' prevalence of fatigue in the community. An alternative approach is to conceptualise fatigue as a 'syndrome' and to define threshold criteria which need to be fulfilled before an individual can be considered to constitute a 'case' of CRF. This is the approach adopted by Cella and colleagues.[48] They have proposed a Diagnostic Interview for Cancer-Related Fatigue Syndrome (DICRFS). In order to be considered a 'case' of CRF syndrome an individual should have experienced 'significant fatigue, lack of energy, or an increased need to rest every day or nearly every day' for 2 weeks in the last month. In addition, cases should have experienced at least five out of nine other fatigue-related symptoms, and the fatigue should have had a significant impact on functional abilities. Furthermore, there should be evidence that the fatigue is a consequence of cancer or cancer treatment and that the fatigue is not primarily the consequence of a co-morbid psychiatric disorder. These diagnostic criteria have now been assessed in a number of clinical studies and have generally been found to be a reliable and robust method to categorise patients.[33,39,49–53] However, the need to exclude patients with a co-morbid psychiatric disorder does not make the criteria particularly useful in a palliative care setting where the prevalence of such disorders is particularly high.[54] Murphy and colleagues reported that although 10/16 (62.5%) palliative care patients had significant fatigue, only two such patients (12.5%) had no evidence of a co-morbid psychiatric disorder and could thus be considered to be 'cases' of CRF syndrome.[33] To exclude rigorously patients with co-morbid psychiatric disorders from a diagnosis of CRF syndrome requires a thorough psychiatric evaluation. Although this may be practical in a research setting it is too time-consuming and resource-intensive to be used as part of a routine clinical assessment.

4. How common is cancer-related fatigue?

As the previous discussion has suggested, the prevalence of fatigue is likely to vary depending upon the assessment instrument used and the 'threshold' above which patients are considered to have 'significant' fatigue. At the most basic level, prevalence can be gauged by asking patients how fatigued they have felt in the previous month. In a multi-centre survey of heterogenous cancer patients, 58% reported that fatigue had affected them 'somewhat', 'quite a bit' or 'very much' in the past month.[32,55] However, the problem with this approach is that it takes no account of the background prevalence of fatigue in the general population. The most reliable data on prevalence comes from studies that have included a control group, have used a fatigue instrument that can be referenced against population norms, or have employed the diagnostic criteria for CRF syndrome. Prue and colleagues have recently undertaken a systematic review in order to determine the prevalence and pattern of CRF.[56] They found that most studies have reported significant increases in fatigue in cancer patients undergoing anti-cancer therapy, with fatigue prevalence varying between 39% and >90%. All of the studies that had included a comparison group of healthy individuals had reported more fatigue in patients than in the general population. Similar results were found when studies concerned with fatigue following completion of anti-cancer therapy were considered. Most prevalence figures varied between 19% and 38%. All of the 11 controlled studies reported greater fatigue levels in patients than in the comparison group. Minton and Stone undertook a systematic review of the prevalence of fatigue in disease-free breast cancer survi-

vors and concluded that there was good evidence of fatigue occurring up to 5 years after completion of adjuvant treatment.[57] Prevalence figures for fatigue in advanced cancer/palliative care populations are more difficult to establish as fewer controlled studies have been undertaken. Kaasa et al. reported that fatigue in palliative care patients was significantly higher than fatigue in the general population (EORTC –Fatigue scores 25 versus 63.2).[38] Stone and colleagues defined 'severe' fatigue in cancer patients as being greater than that experienced by 95% of a healthy elderly control group.[58] Using this definition they reported that severe fatigue occurred in 78% of palliative care patients.

A total of seven studies have been undertaken using the diagnostic criteria for CRF syndrome.[33,39,49–53] The prevalence of the fatigue syndrome has varied from 10% in women with breast cancer prior to adjuvant chemotherapy, to 56% in a group of heterogeneous cancer inpatients.[49,39] Not all of these studies have applied the diagnostic criteria rigorously. For instance, the telephone interviews conducted by Cella and colleagues were not able to confirm the veracity of patients' reports about their cancer history, nor were they able to exclude the presence of co-morbid psychiatric disorders.[50] The study by Fernades et al. included a control group of 25 healthy women and the prevalence of the fatigue syndrome in this group was reported as 20%.[39] The full diagnostic criteria could obviously not be applied to this population because none of the included women had a history of cancer. Inclusion of the diagnostic criteria in future studies will help to build a better picture of the prevalence of fatigue in different cancer populations.

5. What are the causes of cancer-related fatigue?

The underlying mechanism or 'final common pathway' of cancer-related fatigue remains unclear. Indeed it is unlikely that any single mechanism will ever be identified, as the symptom is almost certainly multi-factorial in origin. Although many studies have reported on the correlates of fatigue and have speculated on the cause of this symptom, there have been very few studies that have tested specific hypotheses about the underlying mechanism.

Prue and colleagues reported that most studies of CRF have found little evidence to relate fatigue severity to basic demographic, disease or treatment-related factors.[56] There is some evidence that fatigue is more common in certain diagnostic groups. However, the authors cautioned that methodological weaknesses in the literature prevented general conclusions being drawn.

Numerous studies have reported a close relationship between fatigue severity and psychological distress in cancer patients. Such an association has also been reported in the general population and in patients with other chronic illnesses.[28,46,59–63] However, psychological distress alone cannot explain all, or even most, of the fatigue experienced by cancer patients. Even after rigorously excluding patients with co-morbid psychiatric disorders, the prevalence of fatigue in patients at the completion of adjuvant chemotherapy was 26% in one study.[49] Smets and co-workers reported that while fatigue increased during a course of radiotherapy, there was no concomitant increase in emotional distress.[61,62] Two randomised controlled trials have reported that while paroxetine improves the mood of patients undergoing outpatient chemotherapy, it has no effect on relief of fatigue[64,65] (see below). Taken together these studies suggest that fatigue and depression/psychological distress are related but distinct phenomena.

Insomnia affects between 30% and 50% of newly diagnosed cancer patients and persists for several years after treatment.[66] In a study of 300 breast cancer survivors Savard and colleagues reported that 51% reported insomnia symptoms and that 19% fulfilled the diagnostic criteria for an insomnia syndrome.[67] However, a recent intervention study found that while cognitive behavioural therapy could improve sleep, it did not result in significant improvements in fatigue.[68] This suggests that although the symptoms of insomnia and fatigue are closely related, a simple cause–effect relationship does not exist.

Inactivity from any cause can lead rapidly to muscular and cardio-respiratory de-conditioning. Following a period of prolonged rest, activity levels that were previously well tolerated may be perceived as being excessively fatiguing. If the response to this is to limit activity, rather than gradually to re-introduce it, then the fatigue may be perpetuated indefinitely.[69] This mechanism has been proposed as a cause of 'secondary' fatigue in cancer patients and has led to a number of studies to test whether exercise is a therapeutic option[70] (see below).

Fatigue is a well-recognised symptom of anaemia, and anaemia is a common problem in patients with cancer. Many studies have reported a significant (although modest) association between fatigue severity and haematocrit.[56,58,71–73] Cella et al. undertook a controlled comparison between anaemic and non-anaemic cancer patients and healthy controls and reported that although both groups of cancer patients were more fatigued than the general population, the anaemic patients were significantly worse.[2] However, Lind et al. reported that only 8% of the variation in fatigue scores between cancer patients could be explained by their haematocrit.[72] Fatigue may be due to a reduced number of erythrocytes or due to impaired red-cell functioning. In one small study, Stone et al. investigated whether there were abnormalities in the function of haemoglobin in patients with cancer, compared to control subjects.[74] No differences were found and there was no association between oxyhaemoglobin dissociation and fatigue severity.

A number of authors have suggested that CRF may be related to an elevated or prolonged inflammatory response in cancer patients.[9,75,76] There is conflicting evidence of an altered inflammatory response in patients on treatment. Some studies have demonstrated increased levels of certain cytokines associated with fatigue,[7,77] while others have failed to find any association.[78] A recent quantitative, systematic review has reported a consistent correlation between interleukin 6 (IL-6), interleukin 1 receptor antibody (IL-1ra), neopterin and CRF.[79] There was, however, no significant correlation with IL-1β or TNFα. The studies included in the review all had limitations in the timing, number and range of measures used. The majority of studies were cross-sectional in nature and did not use well-validated fatigue assessment instruments. Fatigue is known to be associated with other

inflammatory or immune-mediated diseases and so this represents a plausible mechanism for generating fatigue in cancer patients, but further research is required to clarify the significance of the reported findings.

Abnormalities in the hypothalamo–pituitary–adrenal (HPA) axis have been proposed as potential mechanisms of fatigue in Chronic Fatigue Syndrome and in cancer patients.[80,81] HPA down regulation has been measured in one small study of cancer survivors.[82,83] There is also evidence of HPA axis disturbances in patients with metastatic disease.[84–86] Other potential mechanisms of fatigue in cancer patients include alterations in muscle metabolism, reflex suppression of somatic motor outflow via activation of vagal afferents, and dysregulation of central serotonin metabolism.[81] None of these hypotheses has yet been investigated adequately.

6. How can cancer-related fatigue be treated?

Three broad approaches to tackling CRF have been investigated and these form the basis for most fatigue management programmes.

6.1. Exercise interventions

A number of systematic reviews have been undertaken and a Cochrane review is underway examining the role of exercise for improving quality of life, physical functioning and fatigue in patients with cancer.[87–90] The trials in this area have been a mixture of resistance and cardiovascular training and trials differ extensively in terms of frequency, intensity and duration.[88] There has been a move away from hospital and equipment-based trials to exercise programmes based at home.[91–95] Much of this work has been carried out in patients on treatment or disease-free survivors – it is therefore unclear how readily these results can be applied to a palliative care population although some pilot work has been undertaken.[96,97]

Currently, there are conflicting data on the role of exercise in the management of CRF. While most studies show that exercise improves physical fitness, there is not always a corresponding improvement in subjective fatigue. This is illustrated by a recent Cochrane review examining the role of exercise in breast cancer patients receiving adjuvant therapy.[87] The meta-analysis demonstrated an improvement in cardio-respiratory fitness but no associated improvement in fatigue symptoms. In another systematic review (not restricted to breast cancer patients), Conn and co-workers demonstrated a small effect size for the reduction in fatigue across tumour groups.[98] However, they included non-randomised studies. This was much less than the effect size seen with physical functioning.

While the literature suggests that exercise is likely to be beneficial, there are still limitations to the quality of the current evidence. The majority of trials have examined small numbers of subjects without control groups or adequate blinding of assessors. It is therefore unclear what the optimum 'dose', type or frequency of exercise should be. There are potentially fewer safety concerns with the use of an exercise intervention than with pharmacotherapy, but care still needs to be taken with particular groups such as those with advanced disease.

6.2. Psychosocial interventions

Broadly speaking, psychosocial interventions include psychological, educational and support group studies. There is a wide variation in study size, design and quality. By their very nature these studies have complex designs and often used mixed methods. A recent systematic review with meta-analysis has been published.[99] The review by Jacobsen et al. identified 24 psychological intervention studies of which 18 could be included in a meta-analysis. These studies were a heterogeneous group that included cognitive behavioural therapy, supportive and expressive therapies and psycho-education. The interventions were carried out both on individuals and in group settings. A large number of the studies were conducted on breast cancer patients and in patients without metastatic disease. The authors reported that the overall quality of many studies was only 'fair' – often limited by an inadequate description of the methods. Overall, the authors reported a small but significant positive effect for psychological interventions when compared to controls.

The systematic review by Jacobsen and co-workers only included studies up to the end of 2005.[99] More recent studies also support the effectiveness of psychosocial interventions. Ream et al. demonstrated a beneficial effect with an educational intervention during chemotherapy.[100] This intensive nurse-led regimen demonstrated a reduction in the distress associated with fatigue and an improvement in mood. However, there was no change in CRF severity. Armes and co-workers undertook an RCT of a behaviourally based psychological intervention in patients undergoing chemotherapy ($n = 60$).[101] They found a significant improvement in fatigue severity and self-reported physical functioning at 1 month after the completion of chemotherapy. While the effect on physical functioning persisted until 9 months after recruitment to the study, the effect on fatigue did not. There was no reduction in fatigue-related distress at any time. Gielissen and co-workers have demonstrated proof of principle for the use of cognitive behavioural therapy (CBT) in fatigued disease-free breast cancer patients ($n = 112$).[102] The treatment group had a significant reduction in fatigue at 6 months compared to waiting list controls. The results of longer term follow up of this cohort demonstrated ongoing positive treatment effects with continued reduction in fatigue levels at 2 years.[103] The role of CBT to treat CRF in advanced disease is unclear. There has been pilot work in training palliative care professionals in CBT techniques but this training was not designed specifically to manage CRF.[104]

6.3. Drug interventions

We have recently conducted a Cochrane review on the drug management of CRF.[105] We analysed all randomised controlled trials of the pharmacological treatment of CRF. Eligible studies included a multi-item fatigue scale as one of the outcome measures. Our results highlighted a lack of well-designed RCTs and robust outcome criteria. Only 27 trials met our full inclusion criteria. Six different classes of drugs were identified: haematopoietic growth factors, psychostimulants, bisphosphonates, anti-TNF-α antibodies, anti-depressants and progestational steroids. When appropriate, meta-analy-

ses were undertaken by drug class. These provided evidence for the use of three agents; methylphenidate (a psychostimulant), erythropoietin and darbopoetin (both haemopoetic growth factors).

Two studies have been undertaken using methylphenidate, one of which did not show a statistically significant effect.[106,107] The total number of patients included in these studies was small (approximately 250) and larger RCTs will need to be undertaken before methylphenidate could be recommended as a treatment for CRF.

The evidence for the effectiveness of erythropoietin and darbopoetin was much more robust and has been supported by other systematic reviews.[108,109] Both agents appear to improve CRF in anaemic patients (haemoglobin <12 g/dl). Most studies have been conducted in patients undergoing chemotherapy. The role of these agents in treating fatigue outside of the specific context of anaemic patients on treatment remains unclear. Cancer-related anaemia (from whatever cause) does not explain CRF entirely. Most benefit is seen with correction of anaemia between 8 and 10 g/dl. Only 20% of any potential improvement in CRF is explained at higher levels.[109] The potential side-effects of these drugs (most notably thrombo-embolic events) may also limit their routine use. This is especially a concern in patients with advanced disease who are already at an increased risk.

The review also demonstrated some important negative results: there was no improvement seen in CRF with progestational steroids or with anti-depressants (paroxetine). This suggests that although fatigue is often associated with depression or cachexia, improvements of appetite or mood do not necessarily result in improvements in fatigue.

7. Professional guidelines

The NCCN first published evidence-based guidelines on the management of CRF in 2000. The guidelines are freely available online and are updated annually.[14] The guidelines provide advice on the management of fatigue in patients on treatment, off treatment and in advanced disease. Most of the recommendations in the guidelines are graded at level 2A (uniform NCCN consensus but lower level of evidence, including clinical experience). It is recommended that patients with moderate to severe fatigue undergo a focused history and clinical examination to address treatable contributing factors (e.g. anaemia, pain, insomnia, malnutrition, emotional distress). Recommendations for specific interventions include the use of exercise, psychosocial interventions (stress management, relaxation and support groups), sleep restoration interventions, treatment of anaemia or a therapeutic trial with methylphenidate.

8. Conclusions

Fatigue is a common and distressing symptom affecting patients with cancer from the time of diagnosis, throughout treatment and into advanced disease. It can also affect disease-free survivors sometimes for years after treatment has finished. Further work is required to understand the pathophysiology of CRF and to develop new treatment approaches. Existing management strategies require further evaluation, ideally using large scale, multi-centre RCTs.

Conflict of interest statement

Dr. Stone received a £15k educational grant from Ortho-biotech (UK) in 2001 to undertake a study of red-cell functioning in patients with cancer.

REFERENCES

1. Ream E, Richardson A. Fatigue: a concept analysis. *Int J Nurs Stud* 1996;**33**(5):519–29.
2. Cella D, Lai JS, Chang CH, Peterman A, Slavin M. Fatigue in cancer patients compared with fatigue in the general United States population. *Cancer* 2002;**94**(2):528–38.
3. Berger AM, Walker SN. An explanatory model of fatigue in women receiving adjuvant breast cancer chemotherapy. *Nurs Res* 2001;**50**(1):42–52.
4. Stone P, Hardy J, Broadley K, Tookman AJ, Kurowska A, A'Hern R. Fatigue in advanced cancer: a prospective controlled cross-sectional study. *Br J Cancer* 1999;**79**(9–10): 1479–86.
5. Cimprich B. Attentional fatigue following breast cancer surgery. *Res Nurs Health* 1992;**15**(3):199–207.
6. Roscoe JA, Morrow GR, Hickok JT, et al. Temporal interrelationships among fatigue, circadian rhythm and depression in breast cancer patients undergoing chemotherapy treatment. *Support Care Cancer* 2002;**10**(4):329–36.
7. Geinitz H, Zimmermann FB, Stoll P, et al. Fatigue, serum cytokine levels, and blood cell counts during radiotherapy of patients with breast cancer. *Int J Radiat Oncol Biol Phys* 2001;**51**(3):691–8.
8. Servaes P, Gielissen M, Verhagen S, Bleijenberg G. The course of severe fatigue in disease-free breast cancer patients: a longitudinal study. *Psycho-oncology* 2007;**16**(9):787–95.
9. Radbruch L, Strasser F, Elsner F, et al. Fatigue in palliative care patients – an EAPC approach. *Palliat Med* 2008;**22**:13–32.
10. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;**85**(5):365–76.
11. Kirsh KL, Passik S, Holtsclaw E, Donaghy K, Theobald D. I get tired for no reason: a single item screening for cancer-related fatigue. *J Pain Symptom Manage* 2001;**22**(5):931–7.
12. Glaus A. Assessment of fatigue in cancer and non-cancer patients and in healthy individuals. *Support Care Cancer* 1993;**1**(6):305–15.
13. Chang VT, Hwang SS, Feuerman M, Chang VT, Hwang SS, Feuerman M. Validation of the Edmonton Symptom Assessment Scale. *Cancer* 2000;**88**(9):2164–71.
14. NCCN. Clinical practice guidelines in oncology. Cancer related fatigue. <http://www.nccn.org> [accessed 8th January 2008].
15. Chalder T, Berelowitz G, Pawlikowska T, et al. Development of a Fatigue Scale. *J Psychosom Res* 1993;**37**:147–53.
16. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 1995;**39**(3):315–25.
17. Cella D. The Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scale: a new tool for the assessment of

outcomes in cancer anemia and fatigue. *Semin Hematol* 1997;**34**(3 Suppl. 2):13–9.
18. Glaus A. Fatigue in patients with cancer. Analysis and assessment. Recent results. *Cancer Res* 1998;**145**(XI):1–172.
19. Hann DM, Jacobsen PB, Azzarello LM, et al. Measurement of fatigue in cancer patients: development and validation of the Fatigue Symptom Inventory. *Qual Life Res* 1998;**7**(4):301–10.
20. Piper BF, Dibble SL, Dodd MJ, Weiss MC, Slaughter RE, Paul SM. The revised Piper Fatigue Scale: psychometric evaluation in women with breast cancer. *Oncol Nurs Forum* 1998;**25**(4):677–84.
21. Schwartz AL. The Schwartz Cancer Fatigue Scale: testing reliability and validity. *Oncol Nurs Forum* 1998;**25**(4):711–7.
22. Stein KD, Martin SC, Hann DM, Jacobsen PB. A multidimensional measure of fatigue for use with cancer patients. *Cancer Pract* 1998;**6**(3):143–52.
23. Mendoza TR, Wang XS, Cleeland CS, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. *Cancer* 1999;**85**(5):1186–96.
24. Hann DM, Denniston MM, Baker F. Measurement of fatigue in cancer patients: further validation of the Fatigue Symptom Inventory. *Qual Life Res* 2000;**9**(7):847–54.
25. Holley SK. Evaluating patient distress from cancer-related fatigue: an instrument development study. *Oncol Nurs Forum* 2000;**27**(9):1425–31.
26. Okuyama T, Akechi T, Kugaya A, et al. Development and validation of the cancer fatigue scale: a brief, three-dimensional, self-rating scale for assessment of fatigue in cancer patients. *J Pain Symptom Manage* 2000;**19**(1):5–14.
27. FACIT. Functional assessment of chronic illness therapy web-site. www.facit.org [accessed 8th January 2008].
28. Bennett B, Goldstein D, Lloyd A, Davenport T, Hickie I. Fatigue and psychological distress – exploring the relationship in women treated for breast cancer. *Eur J Cancer* 2004;**40**(11):1689–95.
29. Tchen N, Juffs HG, Downie FP, et al. Cognitive function, fatigue, and menopausal symptoms in women receiving adjuvant chemotherapy for breast cancer. *J Clin Oncol* 2003;**21**(22):4175–83.
30. Cella D, Zagari MJ, Vandoros C, Gagnon DD, Hurtz HJ, Nortier JW. Epoetin alfa treatment results in clinically significant improvements in quality of life in anemic cancer patients when referenced to the general population. *J Clin Oncol* 2003;**21**(2):366–73.
31. Crawford J, Cella D, Cleeland CS, et al. Relationship between changes in hemoglobin level and quality of life during chemotherapy in anemic cancer patients receiving epoetin alfa therapy. *Cancer* 2002;**95**(4):888–95.
32. Stone P, Richardson A, Ream E, Smith AG, Kerr DJ, Kearney N. Cancer-related fatigue: inevitable, unimportant and untreatable? Results of a multi-centre patient survey. Cancer fatigue forum. *Ann Oncol* 2000;**11**(8):971–5.
33. Murphy H, Alexander S, Stone P, Murphy H, Alexander S, Stone P. Investigation of diagnostic criteria for cancer-related fatigue syndrome in patients with advanced cancer: a feasibility study. *Palliat Med* 2006;**20**(4):413–8.
34. Hwang S, Chang V, Kasimis B. A comparison of three fatigue measures in veterans with cancer. *Cancer Invest* 2003;**21**:363–73.
35. Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *J Pain Symptom Manage* 2002;**24**(6):547–61.
36. Brucker PS, Yost K, Cashy J, Webster K, Cella D. General population and cancer patient norms for the functional assessment of cancer therapy-general (FACT-G). *Eval Health Prof* 2005;**28**(2):192–211.
37. Glaus A, Crow R, Hammond S. A qualitative study to explore the concept of fatigue/tiredness in cancer patients and in healthy individuals. *Support Care Cancer* 1996;**4**(2):82–96.
38. Loge JH, Abrahamsen AF, Ekeberg O, Kaasa S. Hodgkin's disease survivors more fatigued than the general population. *J Clin Oncol* 1999;**17**(1):253–61.
39. Fernades R, Stone P, Andrews P, Morgan R, Sharma S. Comparison between fatigue, sleep disturbance, and circadian rhythm in cancer inpatients and healthy volunteers: evaluation of diagnostic criteria for cancer-related fatigue. *J Pain Symptom Manage* 2006;**32**:245–54.
40. Andrykowski MA, Curran SL, Lightner R. Off-treatment fatigue in breast cancer survivors: a controlled comparison. *J Behav Med* 1998;**21**(1):1–18.
41. Stone P, Hardy J, Huddart R, A'Hern R, Richards M. Fatigue in patients with prostate cancer receiving hormone therapy. *Eur J Cancer* 2000;**36**(9):1134–41.
42. Stone P, Richards M, A'Hern R, Hardy J. Fatigue in patients with cancers of the breast or prostate undergoing radical radiotherapy. *J Pain Symptom Manage* 2001;**22**(6):1007–15.
43. Morriss R, Wearden A, Mullis R. Exploring the validity of the Chalder fatigue scale in chronic fatigue syndrome. *J Psychosom Res* 1998;**45**(5):411–7.
44. Lawrie S, Manders D, Geddes J, Pelosi A. A population-based incidence study of chronic fatigue. *Psychol Med* 1997;**27**:343–53.
45. Loge JH, Ekeberg O, Kaasa S. Fatigue in the general Norwegian population: normative data and associations. *J Psychosom Res* 1998;**45**(1 Spec No):53–65.
46. Pawlikowska T, Chalder T, Hirsch S, Wallace P, Wright D, Wessely S. A population based study of fatigue and psychological distress. *Br Med J* 1994;**308**:743–6.
47. David A, Pelosi A, McDonald A, et al. Tired, weak, or in need of rest: fatigue among general practice attenders. *Br Med J* 1990;**301**(6762):1199–202.
48. Cella D, Peterman A, Passik S, Jacobsen P, Breitbart W. Progress toward guidelines for the management of fatigue. *Oncology (Huntington)* 1998;**12**(11A):369–77.
49. Andrykowski MA, Schmidt JE, Salsman JM, Beacham AO, Jacobsen PB. Use of a case definition approach to identify cancer-related fatigue in women undergoing adjuvant therapy for breast cancer. *J Clin Oncol* 2005;**23**(27):6613–22.
50. Cella D, Davis K, Breitbart W, Curt G. The Fatigue C. Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. *J Clin Oncol* 2001;**19**(14):3385–91.
51. Sadler IJ, Jacobsen PB, Booth-Jones M, Belanger H, Weitzner KK, Fields KK. Preliminary evaluation of a clinical syndrome approach to assessing cancer-related fatigue. *J Pain Symptom Manage* 2002;**23**(5):406–16.
52. Young KE, White CA. The prevalence and moderators of fatigue in people who have been successfully treated for cancer. *J Psychosom Res* 2006;**60**(1):29–38.
53. Van Belle S, Paridaens R, Evers G, et al. Comparison of proposed diagnostic criteria with FACT-F and VAS for cancer-related fatigue: proposal for use as a screening tool. *Support Care Cancer* 2005;**13**(4):246–54.
54. Chochinov HM, Wilson KG, Enns M, Lander S. Prevalence of depression in the terminally ill: effects of diagnostic criteria and symptom threshold judgments. *Am J Psychiatr* 1994;**151**(4):537–840.
55. Stone P, Ream E, Richardson A, et al. Cancer-related fatigue – a difference of opinion? Results of a multi-centre survey of healthcare professionals, patients and caregivers. *Eur J Cancer Care* 2003;**12**:20–7.
56. Prue G, Rankin J, Allen J, et al. Cancer-related fatigue: a critical appraisal. *Eur J Cancer* 2006;**42**(7):846–63.

57. Minton O, Stone P. How common is fatigue in disease-free breast cancer survivors? A systematic review of the literature. Br Cancer Res Treat 2007. doi:10.1007/s10549-007-9831-1.
58. Stone P, Richards M, A'Hern R, Hardy J. A study to investigate the prevalence, severity and correlates of fatigue among patients with cancer in comparison with a control group of volunteers without cancer. *Ann Oncol* 2000;**11**(5):561–7.
59. Byar KL, Berger AM, Bakken SL, Cetak MA. Impact of adjuvant breast cancer chemotherapy on fatigue, other symptoms, and quality of life. *Oncol Nurs Forum* 2006;**33**(1):E18–26 [Online].
60. Loge JH, Abrahamsen AF, Ekeberg O, Kaasa S. Fatigue and psychiatric morbidity among Hodgkin's disease survivors. *J Pain Symptom Manage* 2000;**19**(2):91–9.
61. Smets E, Visser M, Willems-Groot A, Garssen B, Schuster-Uitterhoeve A, Haes JD. Fatigue and radiotherapy: (B) experience in patients 9 months following treatment. *Br J Cancer* 1998;**78**(7):907–12.
62. Visser MR, Smets EM. Fatigue, depression and quality of life in cancer patients: how are they related? *Support Care Cancer* 1998;**6**(2):101–8.
63. Slaughter JR, Slaughter KA, Nichols D, Holmes SE, Martens MP. Prevalence, clinical manifestations, etiology, and treatment of depression in Parkinson's disease. *J Neuropsychiatr Clin Neurosci* 2001;**13**(2):187–96.
64. Roscoe JA, Morrow GR, Hickok JT, et al. Effect of paroxetine hydrochloride (Paxil®) on fatigue and depression in breast cancer patients receiving chemotherapy. *Br Cancer Res Treat* 2005;**V89**(3):243–9.
65. Morrow G, Hickok J, Roscoe J, et al. Differential effects of paroxetine on fatigue and depression: a randomized, double-blind trial from the University of Rochester Cancer Center Community Clinical Oncology Program. *J Clin Oncol* 2003;**21**(24):4635–41.
66. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. *J Clin Oncol* 2001;**19**(3):895–908.
67. Savard J, Simard S, Blanchet J, Ivers H, Morin CM. Prevalence, clinical characteristics, and risk factors for insomnia in the context of breast cancer. *Sleep* 2001;**24**(5):583–90.
68. Savard J, Simard S, Ivers H, Morin CM. Randomized study on the efficacy of cognitive-behavioral therapy for insomnia secondary to breast cancer, part I: sleep and psychological effects. *J Clin Oncol* 2005;**23**(25):6083–96.
69. Wessely S, Hotopf M, Sharpe M. Physical mechanisms of fatigue; fatigue and inactivity. In: Wessely S, Hotopf M, Sharpe M, editors. *Chronic fatigue and its syndromes*. Oxford: OUP; 1998. p. 55–8.
70. Winningham ML, Nail LM, Burke MB, et al. Fatigue and the cancer experience: the state of the knowledge. *Oncol Nurs Forum* 1994;**21**(1):23–36.
71. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage* 1997;**13**(2):63–74.
72. Lind M, Vernon C, Cruickshank D, et al. The level of haemoglobin in anaemic cancer patients correlates positively with quality of life. *Br J Cancer* 2002;**86**(8):1243–9.
73. Glaspy J. Anemia and fatigue in cancer patients. *Cancer* 2001;**92**(6 Suppl.):1719–24.
74. Stone P, Abdul-Wahab A, Gibson J, Wright R, Andrews P. Fatigue in cancer patients is not related to changes in oxyhaemoglobin dissociation. *Support Care Cancer* 2005;**13**(10):854–8.
75. Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and proinflammatory cytokine activity in breast cancer survivors. *Psychosom Med* 2002;**64**(4):604–11.
76. Collado-Hidalgo A, Bower JE, Ganz PA, Cole SW, Irwin MR. Inflammatory biomarkers for persistent fatigue in breast cancer survivors. *Clin Cancer Res* 2006;**12**(9):2759–66.
77. Mills PJ, Parker B, Dimsdale JE, Sadler GR, Ancoli-Israel S. The relationship between fatigue and quality of life and inflammation during anthracycline-based chemotherapy in breast cancer. *Biol Psychol* 2005;**69**(1):85–96.
78. Wratten C, Kilmurray J, Nash S, et al. Fatigue during breast radiotherapy and its relationship to biological factors. *Int J Radiat Oncol Biol Phys* 2004;**59**(1):160–7.
79. Schubert C, Hong S, Natarajan L, Mills PJ, Dimsdale JE. The association between fatigue and inflammatory marker levels in cancer patients: a quantitative review. *Brain Behav Immun* 2007;**21**(4):413–27.
80. Cleare AJ. The neuroendocrinology of chronic fatigue syndrome. *Endocr Rev* 2003;**24**(2):236–52.
81. Andrews PLR, Morrow G, Hickok JT, Stone P. Mechanisms and models of fatigue associated with cancer and its treatment: evidence of pre-clinical and clinical studies. In: Armes J, Krishnasamy M, Higginson I, editors. *Fatigue in cancer*. Oxford: OUP; 2004. p. 51–87.
82. Bower JE, Ganz PA, Aziz N. Altered cortisol response to psychologic stress in breast cancer survivors with persistent fatigue. *Psychosom Med* 2005;**67**(2):277–80.
83. Bower JE, Ganz PA, Dickerson SS, Petersen L, Aziz N, Fahey JL. Diurnal cortisol rhythm and fatigue in breast cancer survivors. *Psychoneuroendocrinology* 2005;**30**(1):92–100.
84. van der Pompe G, Antoni MH, Heijnen CJ. Elevated basal cortisol levels and attenuated acth and cortisol responses to a behavioral challenge in women with metastatic breast cancer. *Psychoneuroendocrinology* 1996;**21**(4):361–74.
85. Spiegel D, Giese-Davis J, Taylor CB, Kraemer H. Stress sensitivity in metastatic breast cancer: analysis of hypothalamic–pituitary–adrenal axis function. *Psychoneuroendocrinology* 2006;**31**(10):1231–44.
86. Rich T, Innominato PF, Boerner J, et al. Elevated serum cytokines correlated with altered behavior, serum cortisol rhythm, and dampened 24-hour rest-activity patterns in patients with metastatic colorectal cancer. *Clin Cancer Res* 2005;**11**(5):1757–64.
87. Markes M, Brockow T, Resch KL. Exercise for women receiving adjuvant therapy for breast cancer. Cochrane database of systematic reviews: reviews. Chichester (UK): John Wiley & Sons Ltd.; 2006 (issue 4). doi:10.1002/14651858.CD005001 [pub2 2006(4)].
88. Knols R, Aaronson NK, Uebelhart D, Fransen J, Aufdemkampe G. Physical exercise in cancer patients during and after medical treatment: a systematic review of randomized and controlled clinical trials. *J Clin Oncol* 2005;**23**(16):3830–42.
89. Stricker C, Drake D, Hoyer K-A, Mock V. Evidence-based practice for fatigue management in adults with cancer: exercise as an intervention. *Oncol Nurs Forum* 2004;**31**(5):963–76.
90. Cramp F, Prue G, Gracey J. Exercise for treatment of cancer related fatigue. Cochrane database of systematic reviews: protocols. Chichester (UK): John Wiley & Sons Ltd.; 2006 (issue 3). doi:10.1002/14651858.CD006145.
91. Dimeo F, Stieglitz R, Novelli-Fischer U, Keul J. Effects of physical activity on the fatigue and psychologic status of cancer patients during chemotherapy. *Cancer* 1999;**85**(10):2273–7.
92. Dimeo F, Rumberger B, Keul J. Aerobic exercise as therapy for cancer fatigue. *Med Sci Sports Exerc* 1998;**30**(4):475–8.
93. Schwartz AL, Mori M, Gao R, Nail LM, King ME. Exercise reduces daily fatigue in women with breast cancer receiving chemotherapy. *Med Sci Sports Exerc* 2001;**33**(5):718–23.

94. Campbell A, Mutrie N, White F, McGuire F, Kearney N. A pilot study of a supervised group exercise programme as a rehabilitation treatment for women with breast cancer receiving adjuvant treatment. *Eur J Oncol Nurs* 2005;**9**(1):56–63.
95. Schneider CM, Hsieh CC, Sprod LK, et al. Effects of supervised exercise training on cardiopulmonary function and fatigue in breast cancer survivors during and after treatment. *Cancer* 2007;**110**(4):918–25.
96. Oldervoll LM, Loge JH, Paltiel H, et al. The effect of a physical exercise program in palliative care: a phase II study. *J Pain Symptom Manage* 2006;**31**(5):421–30.
97. Segal RJ, Reid RD, Courneya KS, et al. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2003;**21**(9):1653–9.
98. Conn VS, Hafdahl AR, Porock DC, et al. A meta-analysis of exercise interventions among people treated for cancer. *Support Care Cancer* 2006;**14**(7):699–712.
99. Jacobsen PB, Donovan KA, Vadaparampil ST, Small BJ. Systematic review and meta-analysis of psychological and activity-based interventions for cancer-related fatigue. *Health Psychol* 2007;**26**(6):660–7.
100. Ream E, Richardson A, Alexander-Dann C. Supportive intervention for fatigue in patients undergoing chemotherapy: a randomized controlled trial. *J Pain Symptom Manage* 2006;**31**(2):148–61.
101. Armes J, Chalder T, Addington-Hall J, Richardson A, Hotopf M. A randomized controlled trial to evaluate the effectiveness of a brief, behaviorally oriented intervention for cancer-related fatigue. *Cancer* 2007;**110**(6):1385–95.
102. Gielissen MFM, Verhagen S, Witjes F, Bleijenberg G. Effects of cognitive behavior therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behavior therapy: a randomized controlled trial. *J Clin Oncol* 2006;**24**(30):4882–7.
103. Gielissen MF, Verhagen CA, Bleijenberg G. Cognitive behaviour therapy for fatigued cancer survivors: long-term follow-up. *Br J Cancer* 2007;**97**(5):612–8.
104. Mannix KA, Blackburn IM, Garland A, et al. Effectiveness of brief training in cognitive behaviour therapy techniques for palliative care practitioners. *Palliat Med* 2006;**20**(6):579–84.
105. Minton O, Stone P, Richardson A, Sharpe M, Hotopf M. Drug therapy for the management of cancer related fatigue. *Cochrane Database of Syst Rev*; 2008. Art No.: CD006704. doi:10.1002/14651858.CD006704.pub2.
106. Bruera E, Valero V, Driver L, et al. Patient-controlled methylphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial. *J Clin Oncol* 2006;**24**(13):2073–8.
107. Fleishman S, Lower E, Zeldis J, Faleck H, Manning D. A phase 2 randomized, placebo-controlled trial of the safety and efficacy of dexmethylphenidate (d-MPH) as a treatment for fatigue and "chemobrain in adult cancer patients. *Br Cancer Res Treat* 2005;**94**:S214.
108. Bohlius J, Wilson J, Seidenfeld J, et al. Erythropoietin or darbepoetin for patients with cancer. Cochrane database of systematic reviews. Art. No.: CD003407(3); 2006.
109. Jones M, Schenkel B, Just J, Fallowfield L. Epoetin alfa improves quality of life in patients with cancer. *Cancer* 2004;**101**(8):1720–32.