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Fatigue in palliative care patients – an EAPC approach

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Fatigue is one of the most frequent symptoms in palliative care patients, reported in .80% of cancer patients and in up to 99% of patients following radio- or chemotherapy. Fatigue also plays a major role in palliative care for noncancer patients, with large percentages of patients with HIV, multiple sclerosis, chronic obstructive pulmonary disease or heart failure reporting fatigue.This paper presents the position of an expert working group of the European Association for Palliative Care (EAPC), evaluating the available evidence on diagnosis and treatment of fatigue in palliative care patients and providing the basis for future discussions. As the expert group feels that culture and language influence the approach to fatigue in different European countries, a focus was on cultural issues in the assessment and treatment of fatigue in palliative care.

As a working definition, fatigue was defined as a subjective feeling of tiredness, weakness or lack of energy. Qualitative differences between fatigue in cancer patients and in healthy controls have been proposed, but these differences seem to be only an expression of the overwhelming intensity of cancer-related fatigue.

The pathophysiology of fatigue in palliative care patients is not fully understood. For a systematic approach, primary fatigue, most probably related to high load of proinflammatory cytokines and secondary fatigue from concurrent syndromes and comorbidities may be differentiated. Fatigue is generally recognized as a multidimensional construct, with a physical and cognitive dimension acknowledged by all authors. As fatigue is an inherent word only in the English and French language, but not in other European languages, screening for fatigue should include questions on weakness as a paraphrase for the physical dimension and on tiredness as a paraphrase for the cognitive dimension.

Treatment of fatigue should include causal interventions for secondary fatigue and symptomatic treatment with pharmacological and nonpharmacological interventions. Strong evidence has been accumulated that aerobic exercise will reduce fatigue levels in cancer survivors and patients receiving cancer treatment.

In the final stage of life, fatigue may provide protection and shielding from suffering for the patient and thus treatment may be detrimental. Identification of the time point, where treatment of fatigue is no longer indicated is important to alleviate distress at the end of life. *Palliative Medicine* 2008; **22:** 13–22.

Key words: fatigue; palliative care; cancer-related fatigue; recommendations

Introduction

Fatigue is a frequent, almost ubiquitous symptom in cancer patients as well as in noncancer patients with progressive life-threatening diseases such as multiple sclerosis, amyotrophic lateral sclerosis or chronic heart or lung disease. Fatigue has a major impact on the quality of life in these patients.

The prevalence and impact of fatigue often have not been recognized by physicians.[1] In a US survey, more than half of the patients reported that they had never talked about fatigue with their physician and the two most frequent reasons for this were the doctors' failure to offer interventions and the patients' lack of awareness of effective treatments.[2]

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However, fatigue has received more attention in recent years, as quality of life has increasingly been used as an endpoint in oncological trials. In addition, research on anaemia and cachexia has provided some insight into the pathophysiology of fatigue. The role of proinflammatory cytokines in cachexia and fatigue is under investigation (reviewed in[3–5]). Cancer trials using erythropoietin found less fatigue with increased haemoglobin levels (reviewed in[6,7]). The National Institute of Health has included fatigue together with pain and depression in their call for increased awareness in symptom management in cancer,[8] and the 6th Framework Programme on Research, Technological Development and Demonstration of the European Union has taken this up in the call for research proposals.

Fatigue also is coming into focus in palliative care research. Pharmacological treatment of opioid-induced sedation with methylphenidate or other drugs has suggested that fatigue may be relieved in palliative care patients.[9,10]

In the light of the increased awareness of fatigue, the question can be raised whether fatigue has reached the point that cancer pain management passed 20 years ago: awareness of the problem leading to clear and easy treatment guidelines, providing adequate symptom relief for most patients. On the other hand, it has been argued that fatigue is fundamentally different from other symptoms, as it may be an inevitable part of the end of life itself.

A consensus position on fatigue is an important first step towards developing recommendations for clinical practice and a research agenda. Recognizing the need for a struc-tured approach, the Research Network of the European Association for Palliative Care (EAPC) has initiated an expert working group on fatigue in palliative care, to provide consensual positions and define areas where consensus is not available.

Methodology

An expert working group of the EAPC met in November 2003 to evaluate the available evidence on diagnosis and treatment of fatigue in palliative care patients. The expert group did not follow a formal consensus process. The expert group also decided against an attempt to produce evidence-based guidelines.

The authors felt that there is not enough consensus on many fatigue topics. Even the definition of fatigue is not used unanimously in trials and publications, preventing comparison of outcomes. Most available evidence on treatment options has been gathered in cancer patients undergoing chemotherapy and it is not clear how much of this data is transferable to palliative care patients. A purely evidence-based approach would also not be able to integrate results from qualitative research, which can provide valuable insights into symptom burden and the need for treatment in patients with fatigue.

The authors decided to present a comprehensive review on fatigue in palliative care patients. This paper represents the position of the working group. It establishes the importance of adequate recognition, assessment and treatment of fatigue in palliative care.

The focus of this paper is on patients with far advanced cancer or at the end stages of other progressive diseases receiving palliative care. The expert group feel that since culture and language influence the approach to fatigue in different European countries, it is important to acknowledge cultural issues wherever appropriate. The expert group formulated statements that reflect consensus in the expert group wherever possible, supported by evidence where available and the need for discussion and further research in other areas.

Draft statements were based on the workshop discussions and refined in an ongoing email discussion among the authors. For each statement, the literature was searched using Medline (Pubmed) and palliative care textbooks by one of the authors (LR) with appropriate search strategies for evidence supporting or refuting the statement. The statements were further refined wherever the evidence necessitated adaptation or change.

Other reviews and expert papers on fatigue in cancer patients have been published recently[11–17] and these reviews will be referred to if possible. Evidence-based guidelines have been presented by the National Comprehensive Cancer Network (NCCN)[18] for cancer patients, collating predominantly nonpharmacological treatment options for fatigue.

Epidemiology and impact of fatigue

Fatigue is one of the most frequent symptoms in palliative care patients, impairing quality of life considerably. Fatigue is reported by not only a majority of patients with advanced cancer, but also many cancer survivors, patients with cardiac failure or with HIV/AIDS.

Fatigue in cancer and noncancer palliative care patients is under-recognized, under-assessed and under-treated.

Fatigue is one of the most frequent symptoms of cancer and cancer treatment. Fatigue (84%), weakness (66%) and lack of energy (61%) were three of the five most frequent symptoms in a study of 1000 patients in an American palliative care program.[19] Fatigue has been reported in up to 99% of patients following radiotherapy or chemotherapy (review in[11,20]). Seventeen to 56% of long-term survivors report fatigue as one of the major symptoms impairing quality of life even months after treatment has ended (review in[11]). In interviews with parents of children who had died from cancer, fatigue was the most common symptom affecting 57% of patients.[21]

Physical fatigue prevents participation in preferred activities and impedes activities of everyday living. Cognitive fatigue complicates activities such as reading or driving a car and thus prevents leisure activities. Fatigue often is associated with affective disturbances and patients feel listless, depressed, irked or paralyzed. In many cancer patients

fatigue impedes quality of life significantly. Patients undergoing chemotherapy rated fatigue as the symptom with the highest impact on daily living, with 91% of fatigued patients stating that fatigue prevented them from leading a 'normal' life.[22] Patients felt that fatigue affected their daily life more than pain after chemo- or radiotherapy, whereas physicians believed that pain adversely affected their patients more than fatigue.[1]

Fatigue also plays a major role in palliative care for non-cancer patients. More than half of the patients with multiple sclerosis describe fatigue as one of their most troubling symptoms (reviews at[23–25]). Fatigue has also been reported for the majority of patients with chronic obstructive pulmonary disease[26] and heart failure.[27] Approximately half of the HIV-patients suffer from fatigue.[28,29] As with cancer-related fatigue, the aetiology often is multifactorial.[30]

Despite being a common symptom, fatigue has not received much attention from palliative care specialists compared with other symptoms such as pain or dyspnoea. Both nonspecialized and specialized physicians frequently consider fatigue as a natural trait of advanced, incurable illness that has to be endured. Treatment options for fatigue are often perceived as scarce and reduction of patient activities is often the only advice given. The consensus group felt that inadequate assessment skills and insufficient knowledge about multidimensional treatment options can lead to non-recognition, under-assessment and under-treatment of fatigue in the vast majority of patients.

Definition of fatigue

As a working definition fatigue is defined as a subjective feeling of tiredness, weakness or lack of energy.
Qualitative differences between fatigue in cancer patients and in healthy controls have been proposed. However, these differences seem to be only an expression of the overwhelming intensity of cancer-related fatigue.

In the nonmedical setting, fatigue can have various meanings. In humans and animals, it can be used as a noun for the 'temporary loss of strength and energy resulting from hard physical or mental work'. In materials (especially metals), it can mean 'the state of being weakened by long stress'. It can also be used as a verb to mean 'to exhaust or tire through overuse or great strain or stress' (http://www.hyperdictionary.com, access date 19 September 2006).

In the medical context of cancer, different definitions have been proposed for fatigue. National Comprehensive Cancer Network defines cancer-related fatigue as a 'distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning' (www.nccn.org/physician_gls/PDF/fatigue.pdf, access date 19 September 2006). A similar definition has been used for fatigue in multiple sclerosis: 'a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities'.[23]

The Oncology Nursing Society defines cancer-related fatigue 'as a feeling of debilitating tiredness or total lack of energy that can last for days, weeks or months; commonly caused by anaemia, fatigue is the side effect of chemotherapy that affects patients the most – more than nausea, pain or depression; symptoms include feeling weak or worn out, having difficulties climbing stairs, walking short distances and performing simple daily tasks; proper nutrition, light exercise, short naps and medications may help alleviate the fatigue' (http://www.cancersymptoms.org/glossary.shtml, access date 19 September 2006).

Glaus has stressed the qualitative difference of cancer-related fatigue to fatigue in everyday life: 'Fatigue in cancer patients is a subjective feeling of unusual tiredness, affecting the body (physical), the emotions (affective) and the mental function (mental), persisting for several weeks and relieved only partially or not at all with rest or sleep. Fatigue in healthy people is a subjective feeling with circadian rhythm, which may be pleasant and normally is relieved by rest'.[31]

Fatigue has also been defined as a clinical syndrome. The Fatigue coalition has suggested the use of the International Classification of Diseases-10 (ICD-10) criteria for the definition of cancer-related fatigue requiring 'significant fatigue, diminished energy or increased need to rest, disproportionate to any recent change in activity level' to be present every day or nearly every day for two consecutive weeks out of the last month (Table 1). Five out of ten additional symptoms

Table 1 Definition of fatigue in the international classification of diseases (ICD-10)[32]

	A1 and at least five out of A2–A11 have been present for most days in at least two consecutive weeks in the past month
A	
A1	Significant fatigue, diminished energy or increased need to rest, disproportionate to any recent change in activity level
A2	Generalized weakness, limb heaviness
A3	Diminished concentration or attention
A4	Decreased motivation or interest to engage in usual activities
A5	Insomnia or hypersomnia
A6	Experience of sleep as unrefreshing or nonrestorative
A7	Perceived need to struggle to overcome inactivity
A8	Marked emotional reactivity (such as sadness, frustration, irritability) to feeling fatigued
A9	Difficulty completing daily tasks attributed to feeling fatigued
A10	Perceived problem with short-term memory
A11	Postexertional malaise lasting several hours
B	The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning
C	Evidence from history, physical examination or laboratory findings, that symptoms are a consequence of cancer or cancer treatment
D	Symptoms are not primarily a consequence of comorbid psychicatric disorders such as major depression, somatization disorder, somatoform disorder or delirium

such as generalized weakness, diminished concentration, insomnia or hypersomnia and unrestorative sleep are required for the diagnosis.[32] The authors emphasize that fatigue must cause significant distress or impairment, is to be associated with cancer or cancer treatment and must not be due to a comorbid psychiatric disorder. This definition is similar to that used for Chronic Fatigue Syndrome (CFS), which has been described as a specific illness in its own right and is probably caused by central nervous dysfunction (review in[33]). The threshold of six symptoms (fatigue and five others) and the time span of at least two weeks have been chosen arbitrarily, with the intention of capturing various causes of fatigue, but so as not to render the diagnosis trivial.[34] The authors found that although 37% of cancer patients reported fatigue for at least two weeks in the previous month, only 17% fulfilled their strict criteria for cancer-related fatigue syndrome. However, since 79% of the patients reported 'debilitating fatigue,'[32] it may be that this rather strict definition of the fatigue syndrome excludes many patients who should have been assessed and treated for fatigue. The International Classification of Diseases-10 criteria have been defined to recognize the fatigue syndrome in all stages of cancer from active treatment to advanced stages as well as to survivorship, but may be of limited value for diagnosis of fatigue in the palliative care setting, where the prevalence of concomitant psychological disorders is high.[35,36]

Some authors state that cancer-related fatigue is qualitatively different from the fatigue that everyone feels after exercise,[32,37–39] and cancer patients report that they are less likely to recover from fatigue during sleep. A self-report described cancer-related fatigue as totally unlike even the most profound fatigue of an otherwise well person.[40] However, the consensus group emphasized that cancer-related fatigue does not seem to be qualitatively different from fatigue in healthy humans, but simply represents one end of a continuum of intensity. Less severe fatigue in cancer patients may also be relieved by rest.

Fatigue is not uncommon in the general population. A prevalence of fatigue up to 28% has been found in unselected patient groups treated by general practitioners.[41,42] Pawlikowska *et al.* looked at the prevalence of fatigue in a general population and found that fatigue is continuously distributed in the community. Substantial fatigue lasting six months or longer was reported by 18% of the respondents.[43] Stone *et al.* defined severe fatigue as an intensity score in excess of the 95th percentile of a healthy control group and found the prevalence of severe fatigue to vary between 15% in recently diagnosed breast cancer patients and 78% in patients receiving inpatient palliative care.[44] Mendoza *et al.* found that healthy controls consistently rated fatigue levels as lower than cancer patients using a variety of different fatigue instruments.[45]

The second edition of the Oxford Textbook of Palliative Medicine uses the concept of asthenia and finds that fatigue is only one of the dimensions of asthenia: 'Astenos (Greek) means absence or loss of strength. Asthenia includes three different major symptoms: (1). fatigue or lassitude defined as easy tiring and decreased capacity to maintain performance; (2). generalized weakness defined as the anticipatory sensation of difficulty in initiating a certain activity and (3). mental fatigue defined as the presence of impaired mental concentration, loss of memory and emotional lability'.[46]

Finally, fatigue has been described not as a clinical symptom, but as a behavioural concept, where the symptom is part of a continuum ranging from tiredness to fatigue and then to exhaustion.[47] These stages are related to defined behavioural patterns. Nonadaptation will lead to progression towards exhaustion, at least in patients with normal haemoglobin levels.

These differences in the concepts of fatigue present an obstacle to producing a common definition of fatigue in Europe. Nevertheless, agreement on a working definition is clearly necessary. The working definition of fatigue should be simple and should take into account that fatigue in palliative care is a symptom that may be caused by the underlying disease, its treatment or by other comorbidities. For this paper, the following working definition is used: Fatigue is a subjective feeling of tiredness, weakness or lack of energy.

This definition corresponds closely to the fatigue subscale of the quality of life questionnaire of the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30 version 3) that is calculated from the three questions 'have you felt weak?', 'were you tired?' and 'did you need to rest?'.[48,49] This pragmatic approach facilitates comparable working definitions in different European languages, as the EORTC QLQ-C30 has been translated and validated in more than 50 languages.

The working definition does not include any qualitative difference between cancer-related fatigue and fatigue in other settings, as the inability to relieve fatigue with rest as well as interference with function seem to be indicators of the intensity of fatigue rather than criteria for the quality of fatigue.

Cancer-related fatigue usually is considered a negative emotion. However, in a German study, two out of 117 patients with chronic pain commented that they found it pleasant.[50]

The working definition relies on the subjective assessment of the patient only. Currently no objective measurement of fatigue is feasible, though objective activity assessment for weakness as a subdimension of fatigue has been proposed. However, as palliative care focuses on the subjective condition of the patient, the subjective assessment should be the indicator for treatment.

There seems to be considerable overlap between fatigue and depression.[51] Weakness and tiredness are among the predominant symptoms of depression and feeling depressed often is part of the affective dimension of fatigue. However, there are some symptoms that are reported only with depression (such as sustained feelings of worthlessness, recurrent thoughts of death) and some symptoms are specific for fatigue (such as postexertional malaise).[51]

There also seems to be some overlap between fatigue and the cachexia and anorexia syndrome, and both may be reported by the patient concomitantly.[52] As with depression, these symptoms represent distinct entities and efforts should be made to assess and treat them separately. However, it has been suggested that investigation of symptom clusters involving fatigue instead of fatigue as an isolated symptom may be the next step in research in symptom control.[53,54]

Pathophysiology of fatigue

Primary fatigue is hypothesized to be related to the tumour itself. This may either be through peripheral mechanisms such as energy depletion or by central mechanisms such as dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis or serotonin metabolism. These mechanisms may ultimately be related to high levels of cytokines.

Cancer-related concurrent syndromes and comorbidities such as anaemia, cachexia, fever, infections or metabolic disorders as well as sedative drugs for symptom control can produce secondary fatigue.

The pathophysiology of cancer-related fatigue is not fully understood. In most patients, throughout the disease trajectory, many different causes will contribute to the development of fatigue.[55] For a systematic approach, the expert group suggests a differentiation between primary fatigue, probably related to high cytokine load and secondary fatigue from cancer- or treatment-related concurrent syndromes and comorbidities (Figure 1).

In advanced cancer, many factors are likely to contribute to fatigue. The relative contribution of each cause will fluctuate throughout the disease trajectory, thus challenging too simplistic primary and secondary concepts in clinical practice. In a quantitative review of 18 studies with 1037 participants, significant positive correlations were found between fatigue and circulating levels of inflammatory markers. However, 31 out of a total of 58 correlation estimates in these studies were not significant.[56]

High cytokine concentrations have been reported in association with fatigue in patients undergoing radio- and chemotherapy as well as in cancer survivors.[57,58] However, another study with women with uterine cancer receiving curative external radiation therapy found no correlation of fatigue intensity and levels of interleukin-1 (IL-1) and tumour necrosis factor (TNF) and even a negative correlation between fatigue and interleukin-6 (IL-6) level.[59]

Simple assessment of circulating cytokine concentrations alone may not be sufficiently reliable. In one study, significantly higher serum levels of markers associated with proinflammatory cytokine activity were found in fatigued breast cancer survivors compared with nonfatigued survivors. These markers included IL-1 receptor antagonist (IL-1ra), soluble TNF receptor type II (sTNF-RII) and neopterin as a

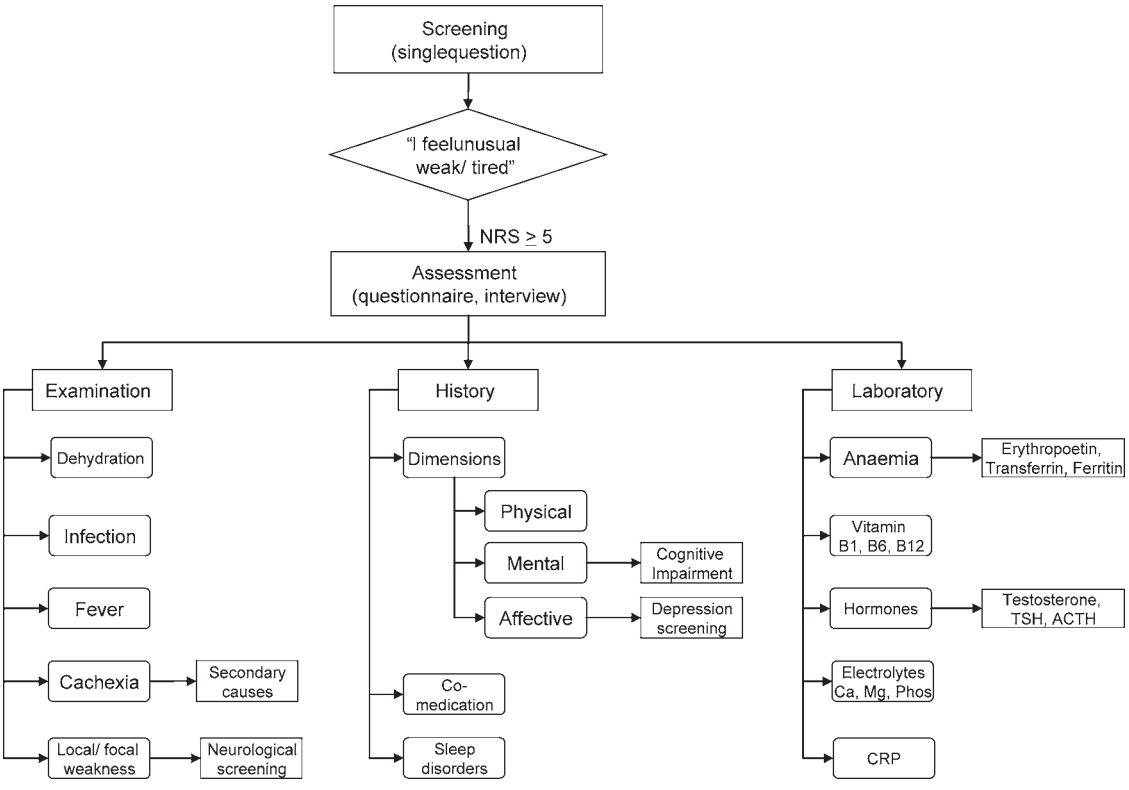

Figure 1 Algorithm for diagnosis of fatigue in palliative care patients.

measure of macrophage activity.[60] Significant correlations between fatigue and IL-1ra and between fatigue and neopterin have been confirmed in a review.[56] However, in survivors from lymphoma with high levels of fatigue 4–10 years after bone marrow transplantation, no correlation of fatigue intensity with cytokine levels or levels of cytokine markers was found.[61] Increased levels of vascular endothelial growth factor and soluble intercellular adhesion molecule-1 (sICAM-1) were related to increased fatigue following anthracycline-based chemotherapy in patients with advanced breast cancer.[62]

The pathophysiology of cytokine-related primary fatigue includes both peripheral and central components. Peripheral mechanisms may be related to energy imbalance, such as altered muscular metabolism and central mechanisms may involve changes in the neural function of the HPA axis and neuronal systems underlying arousal and fatigue.[38]

Peripheral energy depletion following reduced intake of food has been postulated as a cause of fatigue.[63] Adenosine triphospate has been used with good effect on fatigue and cachexia in an open-label, randomized controlled trial,[64] leaving the discussion open whether energy delivery or stimulation of P2 purinergic-receptors caused the effects. It is not clear whether energy depletion in fatigued patients is mainly a manifestation of concomittant cachexia.

Another hypothesis on primary fatigue relies on evidence from animal studies suggesting a reflex circuit with the reduction of somatic muscle tone from vagal afferent stimulation. Intraperitoneal injection of IL-1β induced sickness behaviour with decreased activity and increased sleep in rats and abdominal vagotomy abolished or attenuated this response.[63] However, evidence in support of this vago-somatic inhibitory reflex is scant.

Comparing patients with cancer-related fatigue with healthy volunteers, Davis *et al.* found a reduction of central drive in the cancer group, whereas resting twitch force in the biceps muscle was similar and postfatigue twitch force was even greater in the cancer group, indicating less physiological fatigue in the cancer patients.[65] These results point to a predominantly central change as the cause of cancer-related fatigue.

Dysregulation of the HPA axis has been suggested as a possible central mechanism of primary fatigue. The diurnal cortisol rhythm was subtly, but significantly changed in fatigued breast cancer survivors with a less rapid decline in cortisol levels in the evening hours.[66] Compared with nonfatigued survivors, the cortisol response to stress was blunted in this patient group.[67] Fatigue also may be linked to serotonin metabolism in the brain. The 5-hydroxytryptamine (5-HT) transporter, the main mechanism for removal of 5-HT from the synaptic space, is up-regulated by increased levels of TNF.[63]

Concurrent syndromes and comorbidities may further drain the reduced resources of energy and increase the feeling of fatigue and lack of energy. Proinflammatory cytokines such as IL-1, IL-6, TNF or interferon play a major role in the pathophysiology of cachexia, anaemia, fever and infection, all of which can cause or aggravate fatigue (Table 2).[68]

Cachexia does not only result from reduced nutritional intake, but has been predominantly linked to a profound change in metabolism, with increased proteolysis in skeletal muscle and increased synthesis of acute phase proteins in the liver.[69,70] The involvement of cytokines in cancer-related anorexia and cachexia have been extensively researched (reviews in[4,69]).

Anaemia clearly is a cause of fatigue in cancer patients and anaemic patients are more fatigued than nonanaemic

Table 2 Laboratory parameters for differential diagnosis of fatigue

Comorbidities	Parameter	
Anaemia	Haemoglobin, transferrin, ferritin, iron, erythropoetin	
Electrolytes	Calcium (and albumin), magnesium, phosphate	
Organ dysfunction	Creatinine, bilirubin	
Hypothyroidism	TSH, free T3 and T4	
Infection	WBC (white blood cell count), C-reactive protein	
Hormones	ACTH, cortisol, free testosterone, melatonin	Cortisol requires a 24-h profile
Vitamin deficiency	Vitamin B1, vitamin B6, vitamin B12	
Cytokine load	Interleukin 1, interleukin 6, TNF-α (tumour necrosis factor)	Markers for increased cytokine load might be better suited than cytokines themselves: IL-1 receptor antagonist (IL-1ra), soluble tumour necrosis factor receptor type II (sTNF-RII) and neopterin (macrophage activity marker)

patients.[71] High cytokine levels diminish erythropoetin secretion and blunt the erythropoetin response to cancer-related anaemia. Treatment of anaemia with erythropoetin can result in alleviation of fatigue (reviewed in[6]). However, as the association between haemoglobin level and fatigue intensity is only weak, it has been hypothesized that impaired functionality of the haemoglobin instead of just lower levels may be responsible for fatigue.[72] However, investigating oxyhaemoglobin dissociation as an indicator of the function of the haemoglobin, no differences were found between cancer patients and healthy controls.

Other metabolic disorders such as hypothyroidism, hypogonadism,[73] dehydration or electrolyte disturbances such as hypercalcaemia, hepatic, cardiac or renal failure, sleep disorders, anxiety or emotional stress may contribute to cancer-related fatigue,[74] and treatment of these causes may alleviate fatigue considerably. New anti-neoplastic therapies may be associated with novel causes for secondary fatigue. Hypomagnesaemia following anti-neoplastic treatment with cetuximab, a monoclonal antibody to the epithelial growth factor receptor has been reported recently as a cause of secondary fatigue.[75,76] Depression has been linked with fatigue and fatigue is one of the main symptoms of major depression.[77] Fatigue can also be aggravated by other cancer- or treatment-related symptoms. In a group of breast cancer survivors, fatigue was significantly correlated with dyspnoea, insufficient sleep and depression, with these three variables accounting for a total of 46% of variance in fatigue.[78]

Many drugs with sedative properties regularly used in palliative care such as opioid analgesics, benzodiazepines, anti-depressants or anti-convulsants can add to the fatigue load.

As with cancer, fatigue and sleep disturbances have multiple causes in most patients with HIV infection and AIDS.[30] Increased levels of IL-1 and TNF from HIV infection may lead to sleep disturbances and fatigue (reviewed in[79]). Anti-viral treatment with cytokines may boost fatigue dramatically.[80–83] Anaemia,[84] dysregulation of growth hormone[85] or hypothyroidism[86] have also been implicated in the pathophysiology of fatigue with HIV.

Whereas some work has been done on the pathophysiology of cardiac cachexia,[87] only little research is available on the pathophysiology of fatigue in patients with cardiac failure. Cachexia-related loss of skeletal muscle may contribute to fatigue in these patients. Reduced muscle strength and endurance has been linked to changes in histology and metabolism in patients with chronic heart failure.[88] These changes seem to be related to imbalances of anabolic and catabolic factors. The cause of this shift is not clear, but may be due to continuous haemodynamic stress from decreased peripheral perfusion. Fatigue may be aggravated by the ergoreflex from metabolic stimulation of ergoreceptors in the muscle, causing increased ventilation and sympathetic activation after exercise.

Fatigue in chronic progressive disease has also been described as part of the cytokine-induced sickness behaviour together with other symptoms such as loss of appetite, sleepiness, fever and aching joints.[89] This seems to be a physiological adaptive response reorganizing priorities to facilitate recovery from an infection. Chronic sickness behaviour from inappropriate prolonged activation of the immune system may offer an explanation for chronic fatigue in a wide range of chronic diseases, ranging from Alzheimer's disease to stroke.

Assessment of fatigue

A physical and cognitive dimension seem to be acknowledged by all authors.

Weakness seems to be useful as a paraphrase for the physical dimension and tiredness for the cognitive dimension. Screening for fatigue should include questions on weakness and tiredness such as 'Do you feel unusually tired or weak?' or 'How weak are you?' / 'How tired are you?'

Multidimensional specific questionnaires should be used for research projects on fatigue.

Assessment of fatigue should depend on subjective self-evaluation by the patient, substituted by estimations of carers or medical staff only where self-assessment is not possible. As with the definition of fatigue, various approaches to assessment have been proposed. Fatigue may be regarded as a single symptom, as a symptom cluster or as a clinical syndrome. For the single-symptom approach, single item scales ('do you get tired for no reason?') have been proposed. For the symptom cluster approach, checklists and questionnaires with multiple dimensions have been validated (review in,[90] Table 3). Using the clinical syndrome approach the physician has to assess fatigue with a checklist following the definition of the ICD-10.

Many instruments have been constructed for the symptom cluster approach. Some of these instruments are rather long such as the Functional Assessment of Cancer Therapy – Fatigue (FACT-F)[91] with 47 items (although the 13-item fatigue subscale can be used as a stand-alone questionnaire). The Piper fatigue inventory has recently been shortened to 22 items.[92] The Multidimensional fatigue inventory was constructed with 20 items.[93] Some instruments such as the fatigue subscale of the FACT do not cover the different dimensions of fatigue. The brief fatigue inventory (BFI) was constructed in a similar fashion to the brief pain inventory. It assesses severity and impairment from fatigue using only 9 questions. However, the BFI taps only a single dimension described as 'severity' of fatigue.[45] The EORTC QLQ-C30 includes a subscale on fatigue with three items.[48] The EORTC and FACT quality of life questionnaires and the BFI are available in many languages.

Although there is no generally accepted definition of fatigue, it is widely recognized as a multidimensional construct. Glaus described physical, cognitive and affective dimensions of cancer-related fatigue.[94,95] Other authors have

described interference with function, vigour, mood, reduced activity, reduced motivation or distress from fatigue as additional dimensions of cancer-related fatigue, usually in connection with the development of assessment instruments (Table 3).

A physical and a cognitive dimension seem to be acknowledged by all authors. Weakness seems to be useful as a paraphrase for the physical dimension and tiredness for the cognitive dimension.

However, semantic problems impede the discussion about definitions and assessment tools. Fatigue is inherent only in the English and French languages, but not in other European tongues (Table 4).

In all European countries, fatigue has been used frequently in oncology research and assessment of fatigue has been introduced in many oncology trials. However, it is not clear how much explanation about fatigue patients receive and whether the concept of fatigue is understood by patients with native languages other than English or French. Even if the oncology or palliative care specialist has adequate understanding of fatigue, he may not be able to transfer this knowledge and understanding to a patient who is not familiar with the concept. Patients not included in oncological research will only rarely learn of fatigue.

Translation of fatigue into other languages where the term is not commonly used is not without pitfalls. Glaus *et al.* stated that for German-speaking patients, fatigue would be translated with 'Ermüdung' or 'Ermüdbarkeit', whereas 'Müdigkeit' would rather be equivalent with tiredness.[39] Other European languages may have similar problems with translation.

Even with adequate care in translation, equivalent words in other languages may not always cover the different dimensions of fatigue. Care has to be taken that the translated questionnaire covers the same dimensions as the original versions. Patients in a German validation study clearly related fatigue more with cognitive and affective areas than with physical exhaustion and cut-off points for worst fatigue differed in the German and English versions of the BFI.[50] It should be assumed that translation of fatigue into other languages will find similar differences and problems.

The expert group recommends a differentiated assessment of fatigue depending on the setting. Screening for fatigue in nonspecialized settings such as oncology departments or general practice should be done with single-item questions such as 'Do you feel unusually tired or weak?'.

Screening in specialized services such as palliative care units should include questions on weakness and tiredness as the two main dimensions of fatigue at initial assessment and on regular follow-up. Documentation systems such as the modified Edmonton symptom assessment score[96] or the minimal documentation system[97] that include weakness and tiredness are recommended for routine use in specialized services. Patients with high scores (severe weakness/tiredness, NRS ≥ 5) should receive special attention, to detect reversible causes of fatigue or to identify distress associated with perceived fatigue. If fatigue is a priority syndrome for care, they may be asked to complete a standardized multidimensional questionnaire or (preferably) be interviewed to assess the areas and scope of impairment.

Research projects on fatigue should follow a more detailed approach. Specific questionnaires such as the BFI or the anaemia and fatigue subscale of the FACT should be completed at study entry, before and after interventions and at study completion.

Cognitive impairment may prevent self-assessment with standardized questionnaires. Patients with mild cognitive impairment will be able to self-assess fatigue on simple categorical scales, but patients with moderate or severe impairment may not be able to do so. The expert group recommends assessment of fatigue by carers or staff in these patients, taking into account that carers tend to overestimate and staff tend to underestimate fatigue severity.

Children also may not be able to self-assess fatigue with standardized scales or questionnaires. As with pain assessment, school children and adolescents usually will be able to use the same fatigue assessment instruments as adults, but smaller children will lack the ability for abstract thinking required for the assessment scales. No instruments have been developed for assessment of fatigue in children yet. The expert group recommends assessment by parents or by staff in these children, using behavioural observations such as changes of the sleep-wake times, frequent dozing, continuous lack of interest or concentration difficulties.

The cognitive dimension of fatigue may be tested with psychomotor tests such as finger tapping or more complex methods such as the battery used for assessment of driving ability.[98] However, these tests will only have limited value in a palliative care setting, as cognitive or physical impairment will prevent participation of the vast majority of patients in such tests.

Trying to assess the physical dimension of fatigue with objective measures, for example with an ergometer, has been without much success in patients with advanced cancer. However, newer electronic physical activity meters are currently being evaluated in clinical trials. Using devices that record postural changes and other aspects of physical activity, information about the activity level of patients in a palliative care setting may be obtained. This may signify the beginning of a change from subjective self-assessment of the patient to more complex assessment using subjective assessment of impairment together with objective information on physical and cognitive activity.

Treatment of fatigue

Secondary causes for fatigue should be treated causally if possible. Causal treatment of primary fatigue with anti-cytokine or anti-inflammatory pharmacological approaches is under investigation although is currently lacking both promising results and a favourable risk-benefit relationship.

Table 3 Assessment instruments for fatigue in palliative care

Instrument	Items	Example	Scales	
EORTC QLQ C30 V2.0[176]	Thirty items, among them three questions on fatigue	Did you need to rest? Have you felt weak? Were you tired?	Four-step VRS: not at all, a little, quite a bit, very much	Translated and validated in many languages
FACT – An and F[91]	Thirteen items (FACT-F), Seven items (FACT-An), used together with the 27 items of the FACT-G	I feel fatigued I feel weak all over I am frustrated with being too tired to do the things I want to do	Five-step NRS: 0, not at all; 4, very much	Translated and validated in many languages
Piper fatigue scale[92]	Twenty-seven items, behavioural/severity (six items), affective meaning (five items), sensory (five items), cognitive/mood (six items), five additional items	To what degree is the fatigue that you are feeling now causing you distress? To what degree are you now feeling lively/listless?	Adjective wording scales (22 items), open questions (five items)	Only in English language
BFI[45]	Ten items, intensity (three items), impairment (six items)	Have you felt unusually tired or fatigued in the last week? (yes, no Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right now.	Eleven-step NRS: 0, no fatigue, 10, as bad as you can imagine	English, German and Japanese languages, other translations in the process of validation
Fatigue symptom inventory[177,178]	Thirteen items, intensity (four items), duration (two items): interference with functional status (seven items)	Rate the level of fatigue on the day you felt most fatigued during the past week Rate how much, in the past week, fatigue interfered with your general level of activity	Eleven-step NRS: 0, not at all fatigued; 10, as fatigued as I could be	English and Italian versions
Multidimensional fatigue symptom inventory[179]	Eighty-three items, short form with 30 items (currently tested), general dimension (six items), physical dimension (six items), emotional dimension (six items) mental dimension (six items) vigour (six items)	I feel sluggish My arms feel weak I feel tense	Five-step VRS: not at all, a little, moderately, quite a bit, extremely	English, Estonian, Finnish, French for Canada, Hebrew and Lithuanian language versions
Multidimensional fatigue inventory[93]	Twenty items, general fatigue, physical fatigue, reduced activity, reduced motivation, mental fatigue	I feel fit Physically, I feel only able to do a little I feel very active	Seven-step Lickert Scale: 1, yes that is true; 7, no, that is not true	English, Dutch, French, German, Danish and Swedish language versions
Fatigue assessment questionnaire[95]	Twenty-three items, intensity (three items), physical dimension (11 items), affective dimension (five items) cognitive dimension (three items) sleeping problems (single item)	Did you experience weakness, loss of strength? Did you experience difficulties in concentrating? Did you feel sad?	Four-step VRS: not at all, a little, quite a bit, very much VAS for intensity: I did not feel unusually tired at all – I felt extremely tired, exhausted	English and German language versions
'I get tired for no reason'[180]	Single item	I get tired for no reason	Four-step VRS (none or a little of the time to most or all of the time)	English language only
Rhoten fatigue scale[181]	Single item		Ten-point NRS ((0, not tired, peppy; 10, total exhaustion)	

VRS=Verbal rating scale
NRS=Numerical rating scale
VAS=Visual analogue scale

Table 4 Fatigue equivalents in different European languages

Language	Fatigue	Other translation
English (British)	Fatigue	
French	Fatigue	
Italian	Stanchezza	Tiredness?
German	Ermüdbarkeit, Ermattung	Exhaustion?
Swiss	Müde, Bedusselt	
Portuguese	Fraqueza, Cansaço, Fadiga	Weakness, tiredness, fatigue
Norwegian	Trøtt	
Irish (Gaelic)	Buibhestas	

Most patients will require symptomatic treatment for fatigue with pharmacological and/or nonpharmacological interventions.

In the final stage of life, fatigue may provide protection and shielding from suffering for the patient and treatment of fatigue may be detrimental. Identification of the time point where treatment of fatigue no longer is indicated is important to alleviate distress at the end of life.

The vast majority of patients with cancer-related fatigue do not receive adequate treatment. In a survey of patients after chemo- or radiotherapy, only 27% reported that their oncologist had recommended any treatment for fatigue.[1] This is partly due to barriers to reporting fatigue in the patients, but also to inadequate skills and knowledge of physicians.

Treatment of the underlying cause should be initiated in patients with secondary fatigue (Figure 2). Disease stage and life expectancy have to be considered to balance possible risks and potential benefits of causal therapy.

Taking into account the possible role of cytokines in the pathophysiology of fatigue, there may be a role for pharmacological approaches directed at targeting excessive cytokine concentrations. Thalidomide as an antagonist of TNF has been suggested as a treatment of cachexia in cancer[4,99] and AIDS.[100] Thalidomide showed a beneficial effect on weight loss and quality of life in a single small randomized trial with cachectic cancer patients.[101] However, the cytokine antagonist pentoxiphylline had no significant effect on cachexia in randomized trials in HIV[102] or cancer patients.[103] Thalidomide, pentoxiphylline or other drugs interfering with cytokine synthesis such as rolipram have not been used in clinical trials on fatigue yet and sedation as one of the major side effects of thalidomide makes its use for the treatment of fatigue unlikely. No change in fatigue was reported in the randomized trial of thalidomide for cancer cachexia.[101]

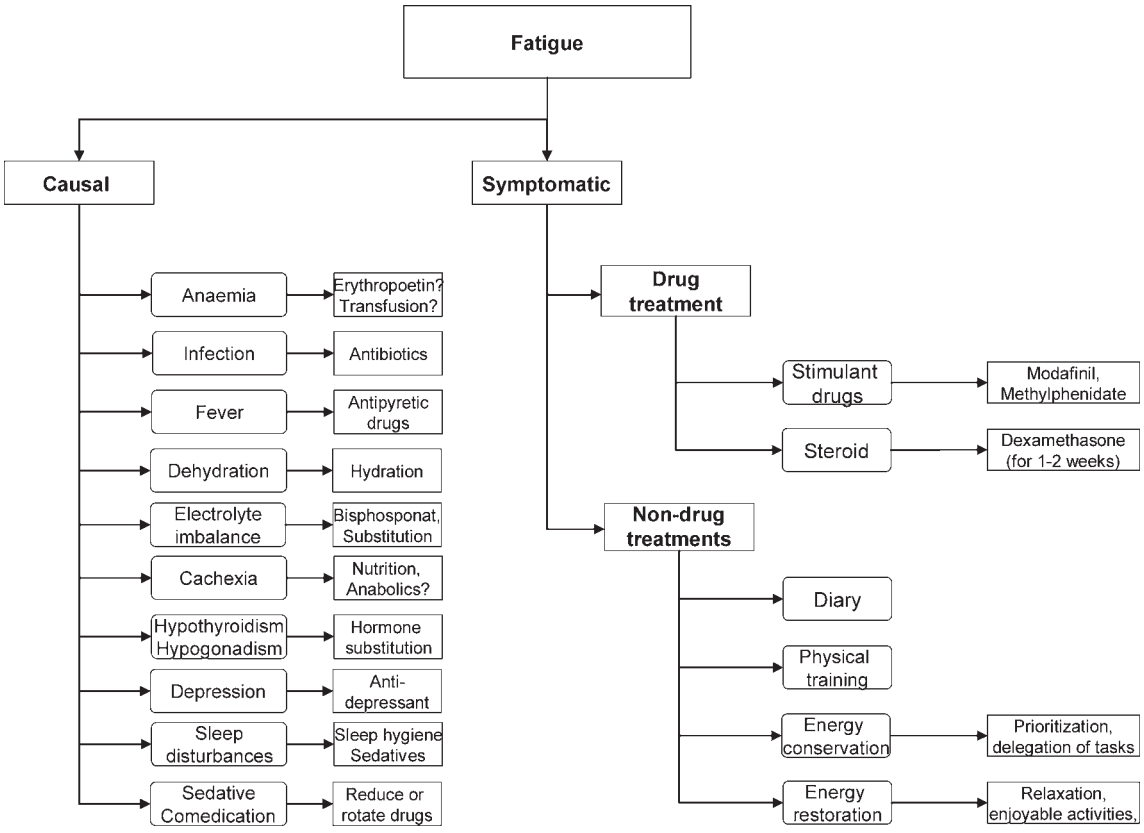

Figure 2 Algorithm for treatment of fatigue in palliative care patients.

For most patients, causal treatment of primary or secondary fatigue will not be effective enough or will take too long. For these patients, symptomatic treatment should be considered. Symptomatic treatment should comprise pharmacological and nonpharmacological interventions.

The expert group discussed the need for treatment with respect to the stage of the patients' illness. It should be kept in mind that in the terminal stage of life fatigue might be considered a 'normal' response, protecting and shielding the patient from suffering and facilitating the transfer from life to death. In the final hours and days of life, effective treatment of fatigue could produce a cruel relapse into the full dramatic experience of the disease when sedation, weakness and emotional deprivation are reduced. Identifying the time point where vigorous treatment of fatigue is no longer indicated is important to alleviate distress at the end of life.

Treatment of secondary fatigue

Treatment of anaemia with erythropoetic agents effectively increases haemoglobin levels, thereby alleviating fatigue, but usually life expectancy is too short in palliative care patients to pursue this option.

The efficacy of treatments for cachexia, depression, fluid or electrolyte imbalances, fever or infection on fatigue have not been investigated, but should be considered in patients with fatigue related to these underlying causes.

Some causes of secondary fatigue such as anaemia, depression, infection, dehydration, malnutrition, hypercalcaemia, hypomagnesiaemia or treatment with opioids or other sedative drugs can be treated and effective causal treatment should alleviate fatigue.

The treatment of anaemia with erythropoetic agents such as erythropoetin or darbepoetin alfa has been a recent focus of interest in oncology. Fatigue has been named as the predominant symptom of anaemia and treatment with erythropoetic agents has been specifically directed to alleviate cancer- and treatment-related fatigue.[104] Randomized trials with darbepoetin[71] and erythropoetin[7,105] have consistently shown reduced levels of fatigue with increasing haemoglobin concentrations. Other reviews have confirmed the efficacy of erythropoetic agents.[6,106] Treatment of anaemia is recommended for cancer patients with haemoglobin levels below 12 g/dL.[107] However, treatment with erythropoetin will take up to 12 weeks to take effect and many patients in palliative care will not have a life expectancy to match this. Considering also the high costs of erythropoetin treatment and potential complications such as thrombosis or pure red cell aplasia, it is not surprising that palliative care physicians seem to make little use of erythropoetic agents.

There was consensus in the expert group that blood transfusions may also increase haemoglobin levels effectively, and may be indicated for palliative care patients with fatigue related to anaemia. The effects of blood transfusions are short-term and transfusions often have to be repeated, sometimes several times per week. Potential transfusion complications, financial and resource burden, all conspire to make routine transfusion unsuitable as a first-line treatment approach. However, in selected patients repeated blood transfusions may have a role in management.

As with blood transfusions, no clinical trials are available for treatment of other secondary causes of fatigue, even though published guidelines stress the importance of causal therapy wherever possible.[74,108]

The use of antibiotics has sometimes been considered controversial in palliative care. In such patients, infection does not always lead to antibiotic therapy. Some palliative care programs will not support the use of antibiotics in their patients, whereas others use them with the aim of symptom control. The expert group stated that treatment of fever or infections with antipyretic or antibiotic drugs may be indicated to treat fatigue-related impairment.

The cachexia-anorexia syndrome (CAS) has been investigated intensively in recent years. However, effective treatment strategies are still scarce. Increasing the caloric intake alone does not seem to improve CAS. Nutritional supplementation with anti-inflammatory polyunsaturated fatty acid or eicosapentanoic acid seems to be beneficial in preclinical and phase II trials (review in[109]). However, three recent randomized trials failed to prove a beneficial effect in patients with CAS.[110–112] Megestrol acetate was shown to improve appetite compared with placebo in several randomized trials[113–115] and compared with dronabinol in one trial.[116] In some of these studies there was also an improvement in quality of life. However, three randomized trials failed to find any benefit for fatigue.[115,117,118]

Cyproheptadine, hydrazine sulfate and cannabinoids have all been suggested as treatments for anorexia but clinical trials have found no benefit for appetite or energy levels (review in[119,120]). Corticosteroids have been shown to increase appetite and daily activity in a randomized trial in advanced cancer patients but with no effect on subjective fatigue.[121] After prolonged treatment with corticosteroids, insulin resistance (aggravating cachexia), proximal myopathy (causing muscle weakness) and increased risk for infections (and cytokine activity) may aggravate fatigue.

Recent data from animal trials have suggested the beta2-agonists clenbuterol and formoterol as potential therapeutic tools for the CAS, probably via an inhibitory effect on the ATP-ubiquitin-dependent proteolytic system of skeletal muscles.[122] Prostaglandin inhibitors such as celecoxib also seem to reverse wasting in the animal model[123] and clinical trials are ongoing. However, the benefit of these drugs on fatigue has not been investigated yet.

As discussed above, there is considerable overlap between depression and fatigue in patients with advanced cancer and treatment with anti-depressants may alleviate fatigue in cancer patients with major depression. However, in a randomized controlled trial, paroxetine did not lead to a reduction of fatigue in patients with breast cancer receiving chemotherapy, even though depression was reduced significantly compared

to placebo.[124] Sedation may be a side effect of anti-depressant therapy, counteracting any potential effects on fatigue.

Other causes of fatigue such as hypothyroidism, dehydration, electrolyte imbalances (eg, hypercalcaemia or hypomagnesemia) or other metabolic disorders should also be treated even though little evidence from randomized trials is available on the efficacy of these treatments. In a randomized trial, comparing 1000 versus 100 ml saline subcutaneously, there was no significant difference in improvement of fatigue between the groups.[125]

Symptomatic nonpharmacological treatment

Aerobic exercise effectively alleviates fatigue in patients receiving cancer treatment.

Other nonpharmacological interventions have been investigated less thoroughly. Strategies on energy conservation and restoration may be useful and counselling for these strategies should be offered.

Nonpharmacological treatment options include provision of information, keeping a diary, energy expenditure planning and physical exercise. Most patients will try to counteract exhaustion and fatigue with prolonged periods of rest.[126] This may even be augmented by healthcare professionals. In a British survey, the most common advice on fatigue was to take more rest and relaxation.[127] However, rest often will not restore energy and persistent reduction of physical activity may even promote fatigue. Counselling on coping strategies should be an effective intervention in these patients.

The effect of physical exercise for cancer patients has been investigated in many clinical trials. Several reviews and meta-analyses have accumulated strong evidence that aerobic exercise will reduce fatigue levels in cancer survivors and patients receiving cancer treatment.[128,129] Recent studies support the use of resistance training or 'anabolic' exercise.[130] However, most trials have been done in patients with breast cancer and good performance status. Only little information is available on patients with far advanced disease and impaired performance status. A 50-min group exercise program twice a week for six weeks reduced fatigue in cancer patients with short life expectancy.[131] The expert group states that these patients are likely to benefit from exercise training, but that training has to be adapted to reduced performance status, for example sessions with sitting up at the bedside several times per day might be considered adequate training for a bedridden patient.

Other nonpharmacological interventions have been investigated less thoroughly. A sleep intervention has been investigated in patients with breast cancer. Using an individualized sleep promotion plan with four components: sleep hygiene, relaxation therapy, stimulus control and sleep restriction techniques patients were able to maintain normal sleep and manage fatigue during chemotherapy.[132]

Other recommendations from guidelines on fatigue have been the keeping of a diary on daily activities and fatigue and counselling for energy conservation principles. Energy conservation should include planning of daily activities with prioritizing of activities. Patients should learn to do the most important things when their individual energy levels are highest and delegate less important tasks to others.[11,37,74]

This should be supported by energy restoration strategies such as ensuring adequate rest and nutrition, reducing stress through meditation or relaxation and participating in enjoyable activities.

Other nonpharmacological interventions have been used for the treatment of fatigue in patients receiving cancer treatment. Clinical trials on the use of aromatherapy and massage,[133] psychotherapy,[134] relaxation therapy[135] or participation in support groups[136,137] have been published. Even when these trials did show some effect on fatigue, it is not clear whether this can be extended to the palliative care setting.

Complex multidimensional intervention programmes may be beneficial compared to more restricted approaches. An intervention designed to minimize or prevent attentional fatigue through regular participation in activities that engage fascination was shown to be effective in two small controlled trials after breast cancer surgery.[138,139] In patients undergoing autologous blood stem cell transplantation, a comprehensive coping strategy programme with counselling, education, written material, an audio tape providing information and instruction in guided imagery and relaxation proved effective compared to the control group.[140] In a randomized study an intervention consisting of an information pack, a fatigue diary and monthly coaching from support nurses who visited patients at home was found to be more effective than the usual support.[141] In another recent paper patients participating in a programme with physical exercise, relaxation and body awareness training and massage reported significant relief of fatigue.[142] However, training comprised 9 h per week for six weeks and the feasibility of such programmes in advanced cancer must be questioned. Only a minority of palliative care patients will be able and willing to spend so much time on a training programme. No studies have been published on the efficacy of training programmes for patients with advanced cancer and impairment of physical and cognitive function.

Symptomatic pharmacological treatment

Treatment with methylphenidate (investigated predominantly in opioid-induced sedation and cancer-related fatigue) and modafinil (in advanced neurological diseases and AIDS) may reduce fatigue.

The efficacy of other stimulant drugs such as pemoline or donepezil as well as the efficacy of corticosteroids on fatigue have been less well investigated.

Research on symptomatic treatment of fatigue in palliative care patients has concentrated on stimulant drugs such as methylphenidate, modafinil, pemoline and donazepil. Although there is evidence from randomized trials on some of these drugs, the routine use of these drugs in palliative care patients was considered controversial in the expert

group. Reluctance to recommend the routine use of stimulant drugs in fatigued patients partly came from the evaluation of available evidence as being too poor, and partly from differences about the concept of fatigue that might not be susceptible to pharmacological treatment.

Methylphenidate is an amphetamine derivate. It acts by enhancing monoaminergic transmitters in the synaptic gap, either by blocking uptake of dopamine or by facilitating catecholamine release.[143] Methylphenidate has been shown to improve cognitive function in patients receiving continuous opioid infusions.[144] Methylphenidate has a rather low bioavailability (11–52%) and a short half-life of ~2 h. After metabolization in the liver the inactive metabolites are excreted renally.

Methylphenidate has been approved for the treatment of depression and of attention-deficit disorder, but is not available in all European countries. Its usefulness for the treatment of depression in palliative care has been described,[145,146] as a fast onset of anti-depressant activity is required for patients with restricted life expectancy.

Methylphenidate has been reported to be effective in several trials for the treatment of opioid-induced sedation[147–149] and for fatigue in advanced cancer patients.[9,150,151] Methylphenidate and exercise both reduced fatigue, increased functional ability and stabilized cognitive function in melanoma patients undergoing interferon treatment, whereas cognitive function deteriorated in the exercise-only group.[152] However, a recent placebo-controlled trial challenged these positive results, as methylphenidate and placebo both improved fatigue with no significant advantage of methylphenidate.[153] Similarly, donepezil was not superior to placebo in a recent randomized trial.[154] With regard to the high placebo response rate, it may be important to identify cancer patients who will benefit from methylphenidate or other drugs more than from other treatment options.

Less information is available on fatigue in noncancer diseases. Methylphenidate and pemoline were effective in the treatment of fatigue in patients with AIDS, with 41% responding to methylphenidate and 36% responding to pemoline compared with a 15% response rate with placebo.[155] In a report on a patient with myotonic dystrophy, methylphenidate improved daytime sleepiness and cognitive impairment.[156] No difference was reported comparing methylphenidate and placebo in elderly patients with fatigue.[157]

Treatment with methylphenidate usually is initiated with 5–10 mg in the morning. With monitoring of response and side effects, the dose may be titrated up to 40–60 mg per day distributed into morning and midday doses. In a recent report patient-controlled oral titration with 5 mg methylphenidate every 2 h as needed showed fast relief of fatigue and other parameters in advanced cancer patients,[10] however, this was not reproduced in a subsequent placebo-controlled trial.[153] Side effects may be dose limiting and include nervousness, jitteriness, agitation and sometimes cardiac side effects such as arrhythmia and tachycardia.

Modafinil acts via the inhibition of GABA, thereby promoting the release of excitatory neurotransmitters such as dopamine, norepinephrine and serotonin in the sleep-wake regulation centres of the central nervous system.[158,159] Modafinil is a racemat with a half-life of ~15 h after multiple dosing. After metabolization in the liver, the inactive metabolites are excreted renally. Modafinil was approved by the FDA in 1998 for the treatment of daytime sleepiness in patients with narcolepsy. In Europe modafinil is released for the same indication.

Modafinil has been used in trials for treatment of fatigue in advanced neurological diseases such as multiple sclerosis,[160–162] amyotrophic lateral sclerosis,[163] myotonic dystrophy[164] Parkinson's diseases[165] and in patients with AIDS/HIV.[166] Modafinil also reduced opioid-induced sedation in a retrospective survey.[167] No direct comparison of modafinil and methylphenidate is available. Only four studies were randomized and blinded.[161,162,164,165] One of these studies did not show any difference against placebo in the relief of fatigue in multiple sclerosis[162] and another one failed to improve daytime somnolence in Parkinson's disease.[165] However, some evidence seems to point towards modafinil as a treatment option for fatigue in palliative care. Studies with modafinil against cancer-related fatigue are currently under way.

A starting dose of 200 mg per day is recommended for modafinil. In some patients titration to effect will be required with dosages up to 400 mg. In older patients or patients with impaired liver function a lower starting dose of 100 mg should be used. Major side effects can be agitation, nervousness, sleep disturbances, nausea or diarrhoea.

Pemoline acts via the same mechanism as methylphenidate, increasing the amount of monoaminergic transmitters in the synaptic gap. Pemoline was as effective as methylphenidate in the treatment of fatigue in patients with AIDS and was superior to placebo.[155] However, potential liver toxicity has limited the use of pemoline.

Donepezil is a centrally acting acetylcholinesterase inhibitor, approved for symptomatic treatment of Alzheimer's disease. Opioid-induced sedation may be related to functional deficits of acetylcholine and preliminary studies with donepezil have suggested at least short-term benefit in patients treated with opioids.[168] Donezepil also was effective for treatment of opioid-induced sedation in an uncontrolled trial.[169] A prolonged elimination half-life of 70 h or more and a high plasma protein binding of 96% may make its use problematic in palliative care patients.

Amantadine, a central acting drug with effects on cholinergic, dopaminergic, adrenergic and glutamatergic neurotransmission has been used for treatment of fatigue in multiple sclerosis in several older, small, placebo-controlled studies, showing modest but significant benefits of this drug (reviewed in[170]).

Anecdotal observation and very limited data from controlled trials support the use of low-dose corticosteroids

in fatigued patients with advanced disease and multiple symptoms.[74] In a randomized trial in patients with advanced cancer, methylprednisolone 32 mg resulted not only in increased appetite, but also in improved daily activity in 21 of 31 patients.[121] Low-dose prednisone in daily doses up to 10 mg led to improvement in several quality-of-life dimensions in patients with bone metastases from prostate cancer.[171] Other randomized trials found no significant benefit on strength[172] and no or only transient improvement of weakness.[173,174] Fatigue was not a primary outcome parameter in these studies and the evidence on the impact of steroids on fatigue is still pending. However, the expert group agreed that the experience in clinical practice is that steroids such as methylprednisolone or dexamethasone are effective in relieving fatigue for a short period of time, usually one or two weeks and that they may be used to alleviate fatigue for well-defined goals, for example allowing the patient to spend a holiday or Christmas time with his family.

Research agenda on fatigue

Research into the underlying pathophysiology of the fatigue syndrome and suitable animal models is paramount as prerequisites for translational clinical research. Basic research should aim for the identification of central and peripheral mechanisms of fatigue in cancer and other diseases.

Basic and clinical research should extend from cancer-related fatigue to fatigue in other patients in the palliative care setting, for example patients with amyotrophic lateral sclerosis or geriatric patients.

A major drawback of the research on fatigue in palliative care is the lack of suitable animal models for fatigue.[38] A model of motivated motor activity has been developed, where mice are trained to run on a wheel voluntarily for extended periods of time. Once trained, the effect of interventions can be monitored.[175] However, compared with the wealth of different animal models in pain research, where studies can be tailored to the pathophysiology of the pain syndrome, a lack of similar models has hampered research on fatigue considerably.

Basic research is required to clarify the role of cytokines and of neurotransmitters in the sleep-wake cycle, and to identify central and peripheral mechanisms of fatigue in cancer and other diseases. Research is also needed on the similarities and discrepancies between fatigue in palliative care and CFS, major depression or cachexia.

Considering that excessive cytokine production is a possible cause of fatigue in cancer patients, it stands to reason that drugs interfering with cytokine synthesis (eg, pentoxiphylline, rolipram and thalidomide) or TNF-antibodies (eg, etanercep and infliximab) or antibodies against other cytokines (eg, anti-IL-6) may become effective treatment options (reviewed for use in cancer-related anorexia and cachexia in[4]). The efficacy of these agents for cancer-related fatigue is currently being investigated in clinical trials, but preliminary results challenge the potential of these drugs as general remedies for fatigue. Future research with these drugs may focus on the efficacy in selected patient groups in palliative care.

Most research on cancer-related fatigue has been done in cancer survivors or patients undergoing chemo- or radiotherapy. Little evidence is available on the efficacy of interventions in the palliative care setting. Interventions such as physical or cognitive training programmes may not be suitable for palliative care patients. For treatment of fatigue in palliative care patients' available interventions should be adapted and specific interventions developed taking into account the limited resources of these patients. There is a need for clinical trials on the efficacy of these interventions in patients with advanced cancer.

Whereas a wealth of information has been published on the treatment of cancer-related fatigue, only limited research has been undertaken on fatigue in advanced cancer patients or in noncancer palliative care patients. As with the pathophysiology of fatigue, specific efforts should be directed towards the investigation of interventions for treatment of fatigue in these groups. This will be even more important considering the increasing percentage of noncancer patients requiring and receiving palliative care in many countries. There will be specific research questions in this area, for example, to what extent diminished energy levels and decreasing physical and cognitive resources might be deemed normal with old age and whether a threshold can be identified where fatigue in the elderly requires assessment and treatment.

Conclusions

This paper of the expert working group of the EAPC has discussed the definition of fatigue and collated the available evidence on assessment and treatment.

Most management strategies have been developed for the treatment of fatigue in survivors or for the treatment of fatigue arising as a side effect of cancer treatment. Transfer of these approaches into clinical palliative care practice is paramount. It is likely that some adaptation to these treatment options might provide relief of fatigue in palliative care patients.

Research on fatigue should focus on the evaluation of the efficacy of available treatment options in the palliative care setting. In addition basic research is needed on the pathophysiology of fatigue, with the aim of identifying new causal and symptomatic approaches to the treatment of fatigue in palliative care.

However, one of the major strengths of palliative care is the consideration of the individual preferences and needs of the patient. This has to be applied to the assessment and treatment of fatigue as to any other symptom in palliative care. The severity and impact of fatigue may change in the course of the disease trajectory. Following guidelines blindly

without consideration may not only be without benefit, but may adversely affect patients. For most patients discontinuation of fatigue treatment in the final stage of life should be discussed. In the terminal stages fatigue may be considered an acceptable final common path, shielding and protecting the patient from what otherwise might be overwhelming emotional and physical distress.

Balancing the impact of fatigue and the advantages and disadvantages of fatigue treatment in the individual situation is an important skill for palliative care specialists and should receive adequate attention in training and clinical practice. Treating fatigue vigorously in those patients who benefit and withdrawing or withholding assessment and treatment procedures from those patients who do not benefit will provide optimal care for the large number of palliative care patients with fatigue.

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