Fatigue in cancer patients – challenges in assessment and treatment

Fatigue is among the symptoms most commonly reported by cancer patients, and has profound impact on the patient’s quality of life and functioning at all stages of the illness trajectory. Fatigue is also a common complaint after successful treatment for cancer, with reported prevalence rates of chronic fatigue (defined as high levels > 6 months) of around 30%.

Despite the increasing interest in fatigue as an acute or chronic symptom, there is still no consensus regarding its content, measurement and classification. Furthermore, there are few evidence-based guidelines for treatment.

The objective of this paper is to provide insight into fatigue as a condition. Central aspects such as definitions, assessment methods and clinical implications are presented, exemplified by studies into long-term Hodgkin’s disease survivors. These issues are essential to the understanding of fatigue, for the interpretation of clinical studies and for the information, treatment and counselling of cancer patients.

Keywords:
cancer, fatigue, measurement, prevalence, self-report

All cancer patients experience fatigue at some time during the illness trajectory, but of varying intensity and duration. Fatigue has negative functional consequences and negative impact on the patients’ quality of life. Patients generally regard fatigue as important, whereas doctors tend not to because fatigue is diagnostically unspecific as it occurs in somatic illnesses, in mental illnesses, and in relation to various psychosocial stressors (1).

The present manuscript is not a comprehensive, systematic review or a meta-analysis of the present knowledge in the area of fatigue, but an attempt to raise the awareness of fatigue, hopefully contributing to improve clinical practice.

One important issue should be kept in mind, however regarding the research on fatigue in relation to health: One part of the research originates from a theoretical perspective, while another is empirically or clinically based. This results in a body of research that is very heterogeneous. Furthermore, fatigue as a concept is poorly understood, as it is experienced by everyone but under various circumstances. This makes it difficult to conduct a theoretical overview that covers the entire field.

Thus, the objectives of this paper are:

• to provide insight into fatigue as a condition, including central issues like
  • definitions
  • mechanisms
  • assessment methods
  • clinical implications

in order to raise the understanding of the condition. This has implications for clininc and research, for example in the interpretation of the literature, in the conduction of clinical studies and for information and counseling of cancer patients. Studies on fatigue in Hodgkin’s disease survivors will be used as examples, because of the homogeneity of the patient population, the high prevalence of fatigue in this group and the number of studies over time that shows the refinement in the assessment methodology during the last two decades.
Definitions of fatigue

The English term fatigue originates from latin (fatigare). Conceptually, it is defined as „extreme tiredness“ (http://www.askoxford.com), but the use is not restricted to the medical field as it is being used in the military, in metallurgy, and in physiology and psychology.

In relation to health, the most frequently used definition of fatigue is „a non-specific and subjective feeling of tiredness, physically and/or mentally“ (2), the underlying definition in this paper.

In neuropsychology and neurophysiology, fatigue is related to

- reduced capacity to perform mental tasks over time, for example during neuropsychological testing
- reduced capacity to sustain force or power output
- fatigability: the experience of fatigue at some point during mental or physical exertion (2).

At present it is uncertain how fatigability and the two other definitions relate to fatigue as a subjective feeling. It is reasonable to assume that fatigued patients also experience increased fatigability, as exemplified in patients with multiple sclerosis (MS) (3).

Fatigue as a subjective experience can occur without muscular or neuropsychological aberrations, and many therefore choose to treat the three definitions as different concepts. Additionally, some authors have used the term asthenia for experiences similar to those defined as fatigue (4). At present it seems as if the term fatigue has become generally more accepted, and asthenia is probably best used as a term for loss of power. Still, there is overlap between the two. This is reflected in the term neurasthenia, which is the correct ICD-10 classification for chronic fatigue syndrome (CFS), while fatigue has not been accepted as an ICD-10 diagnosis.

In clinic and research it is important to distinguish between acute and chronic fatigue. While the first is related to a normal reaction to external stimuli such as chemotherapy, a long, strenuous exercise or a common cold, chronic fatigue relates to elevated fatigue levels of a duration of six months or longer, according to a consensus definition (13).

Mechanisms

From a clinical point of view, each patient will experience fatigue as lack of energy, weariness and tiredness, and as an activity-limiting symptom. The usual clinical approach to symptoms that are reported by patients is to look for underlying pathological processes. However, there is never a direct relationship between a pathological process and a symptom. Hence it is important to make a distinction between the pathological process (the disease) and the subjective experience of disease (i.e. illness) (14), and to acknowledge the psychological and social factors that are involved (15).

No specific neuronal pathway has been demonstrated for fatigue. Because most diseases are ac-
Companied by fatigue, the specificity of fatigue as a symptom is low. In relation to cancer, fatigue may be a symptom of the cancer disease itself, leading to the diagnosis, or a sign of recurrent or metastatic disease. The majority of studies on fatigue in cancer patients have been undertaken during treatment (16) with radiotherapy (17-19), chemotherapy (20) or combined modality treatment (21, 22). In these studies fatigue has been described as a complication to the treatment and correlated with increased symptom distress, impaired quality of life and also reduced survival (23).

Despite the negative consequences, fatigue needs to be accepted as part of the illness experience. Fatigue is probably the most prevalent symptom in advanced cancer, causing considerable distress in these patients. Acute fatigue during active, tumour-directed treatment that subsides over time, seems to have less detrimental effects on quality of life, than persisting high levels after successful treatment, as demonstrated in studies of long-term survivors (24-27), particularly so in Hodgkin's disease survivors (10, 28-31).

As most studies are cross-sectional, no conclusions about the causality of fatigue in cancer patients can be drawn. There is also a lack of studies that have specifically and systematically examined medical late effects in cancer survivors, overt or more subtle, and their association with fatigue. Few studies have explored possible etiologic explanations for fatigue. Hypotheses about Epstein-Barr virus (2), altered immuno- or neuroendocrinological responses (32) and increased cytokine circulation during radiotherapy (33) have been launched but so far, no evidence-based knowledge exists that explains the etiology or underlying mechanisms of fatigue.

**Cytokines**

One example is the poorly understood relationship between cytokines and fatigue, in which a disturbance in proinflammatory cytokines might arise from the disease as well as from the treatment (34, 35). However, no elevated levels of interleukin 6 or soluble TNF receptors (sTNF-p55 or -p75) were found in a sample of Hodgkin's disease survivors (HDSs) with chronic fatigue (26). Cytokines may play a role in sleep regulation, which has particular relevance for fatigue (36). Sleep disturbances like insomnia and hypersomnia are common in cancer patients, but surprisingly few studies have been published (37). One study showed that fatigue during radiotherapy was best explained by the pretreatment level of fatigue, which was highly related to sleep disturbances and sleep-wake patterns (38).

While fatigue itself is commonly taken as a signal to rest, inactivity has negative muscular, cardiovascular and psychological effects, resulting in a “vicious circle” characterized by lowered mood and desire to perform activity, sleep disturbances and increased sensations of fatigue on exercise.

**Endocrinological dysfunction**

Endocrinological dysfunction is rarely investigated in fatigued cancer patients. In patients with chronic fatigue syndrome, the most consistent finding is a low level of cortisol (39), while no associations between gonadal dysfunction, hypothyroidism and fatigue were found in survivors of lymphomas (26, 30). Hypothyroidism is a documented side effect after mantle field irradiation (40). An observational study showed that HDSs who were substituted for biochemical hypothyroidism displayed more fatigue than those who received no medication (30). This may indicate that fatigue in these patients may be related to the underlying disease, rather than to the thyroid dysfunction. In advanced cancer patients no association was found between fatigue and testosterone levels (41).

**Dyspnoea and heart problems**

Dyspnoea may be associated with fatigue, but the exact relationship is not known (42). A recent study in disease-free HDSs treated with chest radiotherapy revealed cardiac abnormalities at screening in 47 of 48 patients (43) suggesting a relationship between asymptomatic heart problems and fatigue. Our clinical experience however, goes more in the direction of a hypothesis of fatigue being associ-
ated with reduced oxygen uptake after mantle field irradiation (30). A possible association between pulmonary sequelae, gas transfer and fatigue is further substantiated by a pilot study in chronic fatigued HDS’s, who participated in an aerobic exercise program for 20 weeks (44). All aspects of fatigue were significantly reduced while the aerobic capacity was significantly improved after the intervention.

**Haemoglobin**

Despite the clinical experience that anemic patients experience fatigue, and that correction of anemia improves functioning and alleviates fatigue, the effect sizes in studies investigating correction of anemia and fatigue are relatively small (45). The fact that most fatigued cancer patients are not anemic, and due to the few controlled studies, there are no consistent findings related to the association between haemoglobin levels and fatigue (16, 41, 46, 47).

**Pain**

Pain is a central symptom in disorders like CFS or fibromyalgia, in which fatigue is a central symptom. In cross-sectional studies of palliative patients, pain has been associated with fatigue (41, 42, 48). However, various analgesic medications like opioids also induces fatigue. Thus, this relationship is complex and may be a confounding effect, meaning that the mechanisms behind fatigue and pain are the same, i.e. the underlying disease (49). Some studies have investigated the effect of pain alleviation upon other subjective symptoms including fatigue. In a study of the effects of immediate and slow-release morphine upon pain, the pain was reduced but fatigue remained unchanged (50).

**Psychological distress**

Chronic fatigue in cancer patients has been related to depression (42), but empirical studies are conflicting (41, 51). It is plausible that psychological mechanisms influence the subjective feeling of exhaustion as in other populations. On the other hand, the literature indicates that fatigue in depressive psychiatric patients is different from the fatigue experienced by cancer patients (52). One study revealed that the patients’ physical condition explained fatigue at start of treatment with radiotherapy, whereas psychological variables did not (51). A reasonable hypothesis may be that the impact of psychological distress on fatigue decreases with increasing somatic morbidity. A recent study from our group showed that chronic fatigue in long-term Hodgkin's disease survivors may be associated with more physical than psychological aspects of long-term cancer survivorship (53). This was based on the significantly better self-reported mental health in the chronic fatigued survivors relative to chronic fatigued subjects in the general population.

Based on the above, it seems reasonable to repeat the well-known fact that fatigue has a multifactorial etiology. It is an unspecified symptom that appears in somatic illnesses, in mental illnesses, and in relation to various psychosocial stressors (1). Thus it should be evident that it can only be measured with a multi-dimensional approach.

**Prevalence of fatigue**

During the last two decades, there has been an increased interest in symptom research as shown in Figure 1. As can be inferred from Figure 1, there has been a considerable increase in the publications regarding fatigue and cancer from 1981 to 2005. This table results from a broad literature search in the PubMed/Medline database combining the MeSH terms „fatigue” and „cancer”, restricted to the fields title or abstract, in English publications, with human subjects. The largest increase was found during the last decade, from 628 „hits“ in the period 1995-1999 to 1316 „hits“ in the period 2000 through 2005. This broad search covers several studies that do not specifically measure fatigue as
an independent study outcome, but nevertheless gives an indication of the increased focus on fatigue in research.

Despite the increased interest in symptom research (Figure 1) and the high prevalence of pain, fatigue, and depressive symptoms in patients with cancer and short life expectancy, these conditions are under-diagnosed and under-treated (54, 55). Because fatigue accompanies most somatic diseases, it is prevalent also in the general population. For example, the Norwegians reporting the poorest health had 30% higher levels of fatigue than the subjects without health problems (56). More than 10% of the general population report substantial fatigue in epidemiological studies (56, 57). Thus it is important to keep in mind that fatigue is not restricted to cancer, when interpreting studies from cancer populations. On the other hand, fatigue is a frequently reported symptom among cancer patients in general (11, 46, 58) and affecting more than 70% of cancer patients with advanced metastatic disease (11, 46).

**Related to diagnosis**

Elevated levels of fatigue have been reported in long-term cancer survivors, and in survivors of Hodgkin’s disease in particular (9, 10, 29, 53, 59, 60-65).

Comparative studies have indicated that fatigue may be more prevalent among survivors of Hodgkin’s disease (HDSs) than among survivors of other cancer types (7, 28, 66).

To examine the body of knowledge on fatigue in Hodgkin’s disease survivors (HDSs), a PubMed/Medline search was performed according to the following criteria: Combining the MeSH terms „fatigue“ and „Hodgkin’s disease“, restricted to the *title or abstract* fields, English publications with abstract, human subjects, adults (19+). Further restrictions included a sample size above 50, and that fatigue was specifically measured as a study outcome.

These criteria yielded the 13 actual studies that are listed in Table 1.

One study comparing relatively large samples of HDSs (n = 249) and testicular cancer survivors (n = 791) showed a significantly higher prevalence of CF in HDSs, 16% vs. 24% (28).

Studies in HDSs that have used fatigue specific questionnaires such as the Multidimensional Fatigue Inventory (MFI) (12) and the Fatigue Questionnaire (FQ) (67) have shown that up to 27% of the patients met the criteria for chronic fatigue (10, 29, 65), which is significantly more frequent than in the general population (10, 65). Whether this is related to specific characteristics of Hodgkin’s disease remains unresolved. However, some reports...
<table>
<thead>
<tr>
<th>Reference</th>
<th>Publ. year</th>
<th>Sample (n)</th>
<th>Study design</th>
<th>Major findings*</th>
<th>Comparison group (n)</th>
<th>Type of measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fobair et al.</td>
<td>1986</td>
<td>403</td>
<td>Cross sectional</td>
<td>37% reported to be tired</td>
<td>None</td>
<td>Single item</td>
</tr>
<tr>
<td>Devlen et al.</td>
<td>1987</td>
<td>90/120</td>
<td>Prospective</td>
<td>30% and 42% of HDSs reported to be tired, not having regained energy</td>
<td>None</td>
<td>Single item</td>
</tr>
<tr>
<td>Bloom et al.</td>
<td>1993</td>
<td>85</td>
<td>Cross sectional</td>
<td>22% reported that the energy had not returned</td>
<td>Testicular cancer survivors</td>
<td>Single item</td>
</tr>
<tr>
<td>Van Tulder et al.</td>
<td>1994</td>
<td>81</td>
<td>Cross sectional</td>
<td>No significant difference in fatigue between HDSs and controls</td>
<td>Healthy controls</td>
<td>SF-36</td>
</tr>
<tr>
<td>Joly et al.</td>
<td>1996</td>
<td>93</td>
<td>Cross sectional</td>
<td>Significantly more HDSs than controls reported chronic fatigue¹</td>
<td>Healthy controls</td>
<td>EORTC-QLQ C30</td>
</tr>
<tr>
<td>Loge et al.²,³</td>
<td>1999</td>
<td>458</td>
<td>Cross sectional</td>
<td>Significantly more HDSs than controls reported chronic fatigue, 26% vs. 10%</td>
<td>General population</td>
<td>FQ</td>
</tr>
<tr>
<td>Kornblith et al.</td>
<td>1998</td>
<td>273</td>
<td>Cross sectional</td>
<td>Significantly higher levels of fatigue in HDSs than controls</td>
<td>Acute leukemia survivors</td>
<td>POMS</td>
</tr>
<tr>
<td>Wettergren et al.</td>
<td>2003</td>
<td>121</td>
<td>Cross sectional</td>
<td>HDSs reported significantly more worries about fatigue than controls</td>
<td>Healthy controls</td>
<td>SEIQoL-DW</td>
</tr>
<tr>
<td>Fossa et al.⁴</td>
<td>2003</td>
<td>458</td>
<td>Cross sectional</td>
<td>Significantly more HDSs than testicular survivors reported chronic fatigue, 24% vs. 16%</td>
<td>Testicular cancer survivors</td>
<td>FQ</td>
</tr>
<tr>
<td>Ganz et al.</td>
<td>2003</td>
<td>247</td>
<td>Prospective</td>
<td>Significantly higher average levels of fatigue than population norms</td>
<td>None</td>
<td>SF-36</td>
</tr>
<tr>
<td>Ruffer et al.</td>
<td>2003</td>
<td>836</td>
<td>Cross sectional</td>
<td>Significantly higher level of fatigue in HDSs than controls</td>
<td>Healthy controls</td>
<td>MFI</td>
</tr>
<tr>
<td>Hjermstad et al.</td>
<td>2005</td>
<td>476</td>
<td>Longitudinal</td>
<td>Significantly more HDSs than controls, 30% vs. 10%, reported chronic fatigue, 50% of HDSs with chronic fatigue recovered over time</td>
<td>General population</td>
<td>FQ</td>
</tr>
<tr>
<td>Hjermstad et al.2006</td>
<td>2006</td>
<td>475</td>
<td>Cross sectional</td>
<td>HDSs with chronic fatigue had significantly better mental health than population subjects with chronic fatigue</td>
<td>General population with chronic fatigue</td>
<td>FQ, SF-36</td>
</tr>
</tbody>
</table>

Description of tools (ref.):
SF-36: Short-form 36, generic quality of life tool (79)
EORTC-QLQ C30: European Organisation for Research and Treatment of Cancer Core Quality of life questionnaire, cancer specific quality of life tool (78)
FQ: Fatigue questionnaire (67)
POMS: Profile of Moods Scale, description of six moods states (81)
SEIQoL-DW: Schedule for the Evaluation of Individual Quality of Life-Direct Weighting, weighting the five most important areas in life (82)
MFI: Multidimensional Fatigue Inventory (12)

* Significance relates to the P-values in each publication 0.01-0.05
1. Two studies; retrospective and prospective including patients with Hodgkin’s disease and non-Hodgkin lymphomas
2. Two other studies in the sample of Hodgkin’s disease survivors not listed (31)
3. Same sample of Hodgkin’s disease survivors
4. Chronic fatigue defined as elevated level for six months or longer

Table 1. Major studies of fatigue in Hodgkin’s disease survivors (HDSS).
have shown that presence of B-symptoms at diagnosis, regardless of stage of disease, was significantly associated with chronic fatigue (10, 29, 61, 65).

**Related to treatment**

A limited number of studies of fatigue in relation to type of treatment are available (11, 16, 29, 46, 62, 68). Comparisons across studies are difficult due to differences in methodology and interpretation is hampered by the lack of control groups. Nevertheless, most studies indicate that fatigue is common during chemotherapy and radiotherapy. A prospective report on fatigue in HDSs showed that combination treatment with radiotherapy and chemotherapy resulted in higher levels of fatigue assessed by the quality of life (QoL) tool SF-36 during the first year as compared to radiation therapy alone, but with similar levels after two years (62). A recent report from our group found no differences in fatigue levels associated with treatment intensity (29).

**Assessment of fatigue**

The various aspects and the complexity of fatigue impose many challenges when it comes to assessment. Instead of asking whether a patient experiences fatigue, the extent and consequences should be assessed. Ideally, patient data should be compared with relevant reference data adjusted for age and gender. Such adjustments facilitate the interpretation of the results as they are known to affect fatigue (56).

**Symptoms and clusters**

Despite the symptom assessment during the last two decades, there is still no consensus on the content, characterization and classification of QoL and subjective symptoms in general (69), as best evidenced in the area of pain (70). These challenges have specific relevance to the assessment of fatigue and become more pronounced with the high correlation of symptoms in clusters, defined as three or more concurrent and related symptoms (71). However, the synergistic effect of multiple symptoms occurring as clusters has rarely been investigated and decisions regarding the terminology for description of symptom clusters and selection of the most appropriate tools for assessment are yet to be made (71). Specific challenges in the assessment of symptom clusters are related to:

- the temporal pattern of the different symptoms
- the relationship between them
- their related and independent functional consequences
- how or if, effective interventions on one symptom affect the other(s).

The complexity of symptom assessment may be exemplified by the relationship between cachexia and fatigue. Fatigue is multifactorial in origin but with cachexia as an important contributor. Pro-inflammatory cytokines and systemic inflammation are linked with hypermetabolism and anorexia in cachectic cancer patients, also impacting on survival (72, 73) but the mechanisms behind fatigue and cachexia are not well understood. This calls for translational research on the biological and subjective levels.

**Assessment methods**

Several measurement techniques have been used throughout the history. These include observation, self-rating and objective tests. The latter is performed with an instrument that counts movements, and the results are produced electronically. However, the number of movements (the validity) corresponds poorly with the subjective experience of fatigue (74).
Self-report

It is generally agreed, that QoL and symptoms are subjective by nature and as such best assessed as self-report by patients (75-77). Several of the multidimensional QoL-questionnaires such as the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30) (78), SF-36 (79), the Functional Assessment of Cancer – General version (FACT-G) (80), as part of the Functional Assessment of Chronic Illness Therapy (FACIT) systems (http://www.facit.org), and others (81, 82) incorporate questions or scales on fatigue.

Lengthy instruments are often not feasible to use in patients with advanced disease, the elderly and the cognitively impaired. Instead, several validated symptom specific inventories that cover the most frequently occurring symptoms in advanced disease have been developed during the last two decades, such as the 10 item Edmonton Symptom Assessment Scale (ESAS) (83), the M.D Anderson Symptom Inventory (MDASI) (84) and different versions of the Memorial Symptom Assessment Scale (MSAS) (85). These shorter instruments do not allow for a comprehensive assessment of fatigue because they primarily measure the intensity of physical fatigue.

Generic vs. specific tools

Self-rating fatigue-instruments can be categorized according to the terminology of QoL-instruments into generic: not specific to a particular population or disease, disease-specific: like EORTC QLQ-C30 (78) for use in cancer-patients, and domain-specific instruments that focus on specific symptoms like psychological distress, pain or fatigue. Most recent generic and disease-specific HRQOL-instruments include fatigue as a separate dimension, but reports show that the fatigue scale of multi-dimensional QoL-questionnaires primarily assess physical fatigue (86).

Fatigue-specific assessment tools

Several unidimensional fatigue assessment tools with numerical or visual analogue scales exist, such as the Fatigue Numerical Scale (FNS) (87), the Visual Analogue Fatigue Scales (VAFS) (88) and the Pearson Buyars Fatigue Feeling Checklist (PBFFC) (89,90). Some of these are early instruments but still used in clinical studies. The validity of single-item assessments is questionable because the wording so strongly influences the answers. For example, feeling tired is reported ten times more often than feeling weak (57). Furthermore, the consequences and the temporal aspect of fatigue are often not assessed. As shown in Table 1, the earlier studies in Hodgkin’s disease survivors (from 1986 to 1993) used single item assessments, while the majority of newer reports used fatigue specific instruments or multiple tools.

The number and types of dimensions in the multi-dimensional tools are debated, and the instruments reflect this. All present fatigue-measures include physical fatigue, which corresponds to the subjective feeling of being exhausted and lacking energy. Several instruments exist all that have been used in studies on cancer patients, like Cancer Fatigue Scale (CFS) (91), Checklist Individual Strength (CIS) (92), Fatigue Questionnaire (FQ) (67), Fatigue Severity Scale (FSS) (93), FACT-F (94) (http://www.facit.org), Fatigue Symptom Inventory (FIS) (95), Multidimensional Fatigue Inventory (MFI) (12), Piper Fatigue Self-Report Scale (PFS) (96) and the Swedish Occupational Fatigue Inventory (SOFI) (18).

Multidimensional tools used for assessment of fatigue in cancer patients

Table 2 presents an overview of multidimensional tools used in clinical studies in cancer patients. The tools were identified through two PubMed/ Medline searches combining 1. „fatigue assessment” and „cancer”, and 2. „fatigue measurement”
Instruments, listed alphabetically (ref.) | Design and rating | Time frame | Content | Interpretation | Developed for
--- | --- | --- | --- | --- | ---
Cancer Fatigue Scale (CFS) (91) | 11 items: 1 „not at all” to 5 „very much” | At present | 3 subscales: physical, affective and cognitive aspects | Sum score, higher scores indicate more fatigue | Cancer patients
Checklist Individual Strength (CIS) (92) | 20 items: on 7 point Likert scales | Past 2 weeks | 4 subscales: severity 8 items, concentration 5 items, motivation 4 items, physical 3 items | Higher scores indicate more fatigue | Patients with chronic fatigue syndrome
Fatigue Questionnaire (FQ) (67) | 11 items: 0 „better than usual”, 5 „much worse than usual” | Past week | 2 subscales: physical fatigue (PF) 7 items, mental fatigue (MF) 4 items. Additional items on duration and extent for chronic fatigue | Sum scores for PF, MF and total fatigue, higher scores indicate more fatigue | Community and primary care studies
Fatigue Symptom Inventory (FIS) (95) | 13 items, 11 point scale: 0 „not at all”, 10 „extreme”/ „entire day” | Past week and at present | 3 subscales: intensity 4 items, interference duration 2 items | Higher scores indicate more fatigue | Cancer patients
Functional Assessment of Cancer Therapy Fatigue Scale (FACT-F) (94) | 13 items: 0 „not at all”, 4 „very much” | Past week | Prevalence and interference | Higher scores indicate more fatigue | Multidimensional assessment in cancer
Multidimensional Fatigue Inventory (MFI) (12) | 20 items: 1 „no, that is incorrect”, 5 „yes, that is correct” | At present | 5 subscales: general, physical and mental fatigue, motivation, activity | Sum scores for each scale, higher scores indicate more fatigue | Cancer patients
Piper Fatigue Self-Report Scale (PFS) (96) | 22 items, 10 point scales: generic scale: „none”, „a great deal”. Specific scales: „able to concentrate”, „unable to concentrate” | Past week | 4 subscales: behaviour/severity, affective, meaning/sensory, cognitive/mood | Higher scores indicate more fatigue | Cancer patients
Swedish Occupational Fatigue Inventory (SOFI) (18) | 25 items: 0 „not at all”, 6 „to a very high degree” | The last days | 5 subscales: lack of energy, physical exertion, physical discomfort, lack of motivation, sleepiness | Higher scores indicate more fatigue | Occupational fatigue

Table 2. Multidimensional, fatigue specific tools used in clinical studies in cancer patients, 1986–2006.

The tools were identified through two PubMed/Medline searches combining 1. „fatigue assessment” and „cancer”, and 2. „fatigue measurement” and „cancer”, abstracts were reviewed and original publications retrieved.

and „cancer”, restricted to publications in English through 2005. The searches produced 504 and 251 „hits” respectively. Duplicates were deleted, all abstracts were searched, the specific tools were identified and the original publications were retrieved to provide the details listed in Table 2.

Although some of the fatigue specific instruments are developed for use in cancer patients (Table 2), there are no empirical data supporting the need for cancer-specific measures. To aid in the interpretation of research results or to choose an instrument for use in clinical studies, a careful
Consideration of the various properties of the tools must be undertaken. Because different instruments measure different aspects of fatigue, the choice of instrument should be based on the purposes of measuring fatigue in a given situation.

Severely ill patients or patients in a terminal phase may not be able to complete lengthy instruments, while the intention in a follow-up study of long-term survivors may be to capture the functional consequences and temporal and behavioural aspects, not only the intensity. As can be inferred from the above, there is no single measure that stands out as the optimal one for both practice and research. This underlines the necessity of carefully weighting the various tools with respect to:

- the characteristics of the actual population
- the importance of the outcomes for clinic and research
- the administrative feasibility
- ethical issues that may arise
- the psychometric properties (validity, reliability, responsiveness to change over time)
- former use in similar populations
- the existence of reference data to facilitate interpretation.

As a thumb rule, the multidimensional tools are preferable to the unidimensional ones, unless a simple assessment of presence or intensity is warranted. A comprehensive assessment provides a better understanding of the condition and its undesirable consequences for the individual. Furthermore, simply asking about the presence of a symptom yields prevalence rates of little clinical relevance.

Clinical implications

Adequate symptom assessment is the prerequisite for good symptom treatment. Systematic monitoring of subjective symptoms such as fatigue raises the awareness of these problems in clinical practice and should be part of the routine in the medical follow-up of cancer survivors. Subjective issues are often not brought forward by patients, as shown in a study revealing that 52% of patients with fatigue did not report this in their consultation (21).

Furthermore, the collected symptom data must be available at the site of decision making in order to improve treatment. This means that assessment tools should be used routinely in oncology to ask patients about fatigue, pain and depression. In this respect it is important to remember that education of health care providers is essential in order to overcome the conceptual and attitudinal barriers towards subjective symptom assessment, and to enhance the staff’s familiarity with the assessment tools.

Interventions

At present, there is little evidence-based treatment for alleviation of fatigue in cancer patients in general, other than to treat the underlying cause if identified, and symptomatic treatment if necessary. This includes assessment and treatment of pain, assessment of possible poly-pharmacological interactions, correction of anemia, endocrinological and metabolic deficiencies and depression, psychological intervention when necessary and physical exercise (97).

Cognitive behavioural therapy has a documented effect in patients with chronic fatigue syndrome (98) but no systematic studies in cancer patients exist. The results from the pilot study with aerobic training (44) are interesting, but need to be replicated in larger samples. Encouraging patients to engage in moderate aerobic activities rather than to rest the majority of the day is recommended. However, it might be that physical training per se is effective only in a subset of patients with CF as discussed in a recent review (99).

Maybe the devil’s advocate would ask: „Why bother to measure fatigue as it is so difficult to define and assess and so little therapy exists?” The answer is that the high prevalence, the detrimental effects, the unawareness and the apparent under-
treatment makes it a significant clinical commitment to find out more.

However, our present knowledge may well be used to inform and counsel patients about what to expect, under and after treatment. A recent longitudinal study showed that more than 50% of long-term survivors (median follow-up 195 months) had recovered from chronic fatigue during the years between assessments (29), supportive to the study showing that treatment related fatigue subsides over time (62). Further, our clinical impression is that fatigue for most patients is more tolerable given appropriate assessment and counselling. The latter should focus on health-promoting activities such as graded exercise but also on the balance between rest and activity for the individual patient.

Thus, the clinical approach may be guided by the following questions:

- Have a patient-centered focus
- Take the patient's own description seriously
  - How did it start – what were the related circumstances?
  - Development over time – fluctuations?
  - What makes it worse – what makes it better?
- Biological and bodily rhythms, sleep patterns
- Physical activity patterns?
- What is the most plausible explanation?
- Is there an obvious site for intervention?
- Intensity of the symptom, assessed uni- or multidimensionally?
- What level of fatigue is acceptable given the circumstances?
  - For long-term survivors, during treatment, in a palliative phase?
  - The natural course, is improvement expected?
- The important question is not if the patient is tired, but how tired, for how long?

Our recommendations for future research are in line with the recommendations set forth by others (97, 100): The assessment methods need to be refined employing a multidimensional approach, the cancer samples should to be more diverse with respect to diagnosis, age, gender, stage of disease and other disease- and/or potentially fatigue-related variable in order to be more representative. Studies on the effects of various interventions (exercise, pharmacological, psychosocial) must be conducted in a clinical setting, preferably as randomized or controlled studies with adequate sample sizes and standardised outcome measures.

The concluding remarks are related to fatigue being a prevalent and under-assessed condition. However, fatigue is experienced by all cancer patients in varying degrees with negative functional consequences. At present our knowledge is limited, and there is a need to refine and develop further the assessment methods and to enhance the clinical awareness of this condition. A better understanding of the fatigue phenomenon and its mechanisms can possibly improve clinical practice.

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