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REVIEW ARTICLE

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Fatigue, depression and quality of life in cancer patients: how are they related?

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Abstract In a study concerning a group of cancer patients undergoing radiotherapy three research questions were addressed. (1) Is fatigue a valid criterion for depression in these somatically ill patients? (2) What is the 'cause-and-effect' relation between fatigue and depression? (3) To what extent are fatigue and depression related to patients' quality of life. A heterogeneous sample of cancer patients ($n = 250$) were interviewed before treatment, 2 weeks after treatment and 9 months later. Fatigue was measured using the MFI, a self-report instrument covering five dimensions of fatigue. Depression was assessed with the non-somatic items of the CES-D. Quality of life had to be indicated on a Cantrill ladder. Fatigue and depression do not follow the same course over time. Just after radiotherapy, fatigue had either increased or remained stable, depending on the dimension under consideration. Depression, in contrast, decreased. Nine months later fatigue had decreased, whereas levels of depression remained stable. Concurrent relations between fatigue and depression were mostly moderate. There was no strong evidence for a cause-and-effect relationship between depression and fatigue. Depression showed highest concurrent relationships with quality of life, especially before treatment. Prospectively, depression and the dimension of physical fatigue were the main predictors for quality of life. Fatigue is not a valid criterion for depression in these patients. Nor is there a strong cause-and-effect relationship. Both depression and physical fatigue are relevant to patients' quality of life.

Key words Fatigue · Depression · Quality of life · Cancer · Radiotherapy

Introduction

Fatigue is without doubt the most frequently reported symptom in cancer patients [11, 20, 22]. It is also known to have quite an impact on the wellbeing of patients. Aaronson et al. [1] and Hürny et al. [12], for instance, found a negative influence of fatigue on quality of life. In our study, almost half the cancer patients reported fatigue to be one of the most distressing symptoms they experienced [25]. Despite its high prevalence and its consequences for the patients' wellbeing, however, very little research has been devoted to this symptom. A literature search using MEDLINE for the period 1980–1991 by Smets et al. [22] yielded only nine references that included the keywords cancer and fatigue. Although at the moment interest in fatigue appears to be growing, its determinants in cancer patients are still largely unexplored, as are its consequences, including its relevance to the patients' quality of life.

Studies that address fatigue typically investigate both somatic and psychological factors. A psychological

factor that attracts relatively a good deal attention in this respect is depression [2, 6, 16, 18]. Although less frequently reported than fatigue, feelings of depression are common in cancer patients. Most studies report a prevalence of about 20–25% [11, 13, 15]. However, these figures do vary, depending on, for instance, the kind of assessment that is used [15, 18, 21]. Several risk factors predispose patients with cancer to depressive disorder. These include medical factors (site and clinical course of disease, type of treatment, presence of pain, medication), psychological factors (coping ability, developmental life phase, prior mood disorders) and social factors (availability of support, socio-economic pressures) [15].

It is beyond doubt that depression and fatigue are related (e.g. [18]). However, the interpretation of this relation in somatically ill patients is complex. One factor pertaining to this complexity is that fatigue is not only a symptom of many somatic illnesses, but is also one of the key symptoms of depression. Bearing this in mind, the question arises as to whether fatigue in somatically ill patients can be used as a valid criterion for a diagnosis of depression.

Another factor that contributes to the complexity is the issue of causality. Fatigue may be the result of depressed mood. However, the person who continuously perceives his or her energy as insufficient may become depressed. To complicate matters, in cancer depression and fatigue may co-occur without having a causal relationship, because they can both originate from the same pathology. For example, small cell lung cancer and medullary thyroid carcinoma produce hormones that can affect mental function and mood [19]. These complexities have their consequences for both clinical practice and research.

In clinical practice, the problem of interdependency seems to be acknowledged. As a solution, in general more emphasis is laid on the mood component of depression. From this perspective, the symptom of anhedonia, that is the loss of interest or pleasure in everyday pastimes and activities, is found to discriminate best between chronic fatigue and depression in the case of cancer [27]. Besides anhedonia, feelings of helplessness or hopelessness, loss of self-esteem, feelings of worthlessness and a death wish seem to be reliable diagnostic indicators for depression in cancer patients [15]. More somatic manifestations of depression are not totally discarded, however. For instance, because many symptoms related to depression are most prevalent in the morning [5, 7, 26], the time of day when fatigue is worst can be considered relevant. In addition, if a somatic symptom is far more pronounced than can be expected on the basis of the somatic illness, this might be suspected to be related to depression.

Also from a researcher's point of view, the question should be addressed as to what part somatic symptoms, such as fatigue, play in the assessment of depression in somatically ill patients. However, the issue is not commonly taken account of in studies investigating depression in cancer. An attempt to address of this methodological problem was made with the development of The Hospital Anxiety and Depression Scale (HADS) [27]. In line with clinical practice, this scale is based on non-somatic symptoms only, with a heavy reliance on the symptom of anhedonia [27]. A related approach is to use a standard depression questionnaire but excluding the somatic symptoms.

In our study we investigated fatigue in cancer patients who were undergoing radiotherapy. Therefore, it was considered relevant to know what role depression played in relation to fatigue. Questions we addressed in this context were (a) Can fatigue be considered a valid criterion for depression in this group of patients? (b) What is the cause-and-effect relationship between fatigue and depression? However, knowledge of the aetiology and course of such symptoms as fatigue and depression is not an end in itself. Symptoms are relevant, to the degree that they negatively influence patient's quality of life. This leads us to the third research question. (c) To what extent are fatigue and depression linked to quality of life?

To answer these research questions we studied the course of fatigue and depression, assessing them before radiotherapy, after radiotherapy, and again 9 months later. It was hypothesized that if fatigue in this population is a valid criterion for depression, these two symptoms would show the same course over time. Furthermore, concurrent relationships were investigated. To support the validity of fatigue as a criterion for depression, these relationships should be high and stable over the three moments of assessment. It was also checked whether the patients with fatigue most intense in the morning showed high levels of depression. Prospective techniques were used to study the possible causal links between both symptoms. As was stated earlier in the Introduction, these links could be expected to go in either direction. Regarding the research question on quality of life, again concurrent and prospective relationships were analyzed. On this subject, no hypotheses are specified.

Patients and methods

Sample and data collection procedure

Consecutive cancer patients scheduled for radiotherapy treatment at the Academical Medical Centre in Amsterdam were approached. Eligible patients were aged 18 years or older; receiving treatment at an out-patient basis for cure or control of cancer, rather than for palliation; free of malignancy in the central nervous system; not receiving chemotherapy; and native Dutch citizens.

The radiation oncologist introduced the study at the first consultation with written information describing purpose and procedure. Patients were later contacted by telephone by the researchers to ask for consent. Patients who declined participation were requested to rate their fatigue to check for selection bias.

Participants were interviewed at their homes approximately 2 weeks before the start of treatment (T1), 2 weeks after completion of treatment (T2), and 9 months later (T3). Patients receiving additional cancer treatment after the post-treatment assessment were excluded from follow-up.

Instruments

The diagnosis was obtained from the patient's medical chart in each case. The following data were collected on interview: sociodemographic information including gender, age, marital status and education last completed, the presence of co-morbidity, the time of most intense fatigue during the day (no clear pattern, early morning, noon, afternoon, late afternoon, evening) and the first, second and third most distressing symptom of the foregoing week.

Fatigue was assessed with the Multidimensional Fatigue Inventory (MFI-20), which is a self-report instrument consisting of five scales measuring general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue [23, 24]. Psychometric properties have been found to be good.

Depression was measured using part of The Centre for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). The CES-D is a frequently used scale designed to measure depressive symptomatology in the general population. To avoid any overlap in symptomatology with the MFI, we used this scale with the exlusion of the factor 'somatic and retarded activity' [17]. This concerned 14 items, in this paper referred to as the mood component of depression. Scores on this mood component could range from 0 to 42. Cronbach's alpha for this component was found to be 0.82. The items of the CES-D and the component to which they belong are shown in Table 1.

A patient's perception of *overall quality of life* was assessed using a Cantrill ladder [4] ranging from 0 (at the bottom, indicating worst quality of life imaginable) to 10 (at the top, indicating the highest quality of life imaginable).

Statistical analyses

Differences in mean scores over time on the CES-D and the fatigue scales were tested using paired *t*-tests on all cases available. Pearson correlations were calculated to indicate concurrent associations. To determine the predictive power of depression on fatigue and vice versa, regression analyses were performed on the separate fatigue scales and the mood component of the CES-D. The predictive power of fatigue and depression on quality of life was determined by a stepwise regression analyses with the five fatigue scales, and the mood component of the CES-D as predictors.

Table 1 Items in the Centre for Epidemiologic Studies Depression Scale (CES-D) and the component they belong to (somatic = somatic and retarded activity)

Items CES-D	Component
1. I felt that I could not shake off the blues even with help from my family and friends.	Mood
2. I felt that I was just as good as other people.	Mood
3. I felt depressed.	Mood
4. I felt hopeful about the future.	Mood
5. I thought my life had been a failure.	Mood
6. I felt fearful.	Mood
7. I was happy.	Mood
8. I talked less than usual.	Mood
9. I felt lonely.	Mood
10. People were unfriendly.	Mood
11. I enjoyed life.	Mood
12. I had crying spells.	Mood
13. I felt sad.	Mood
14. I felt that people dislike me.	Mood
15. I was bothered by things that usually don't bother me.	Somatic
16. I had trouble keeping my mind on what I was doing.	Somatic
17. I did not feel like eating; my appetite was poor.	Somatic
18. I felt that everything I did was an effort.	Somatic
19. My sleep was restless.	Somatic
20. I could not get going.	Somatic

Results

Sample

Of the 308 eligible patients, 250 (81%) agreed to participate. In Table 2, sociodemographic and medical information on these patients is presented. Fourteen patients (6%) who were not available for pre-treatment assessment agreed to complete the subsequent assessments. Post-treatment assessment included 216 patients (86%); 9 patients (4%) had declined further participation, and 25 patients (10%) were not included in the second assessment for medical reasons, such as receiving additional chemotherapy ($n = 18$) or because they could not be interviewed within the time limit of 1 month post-treatment ($n = 7$). At follow-up, the sample comprised 169 patients, 18 patients (7%) had died, 22 patients (9%) were excluded because of additional cancer treatment following radiotherapy, 4 patients (2%) had declined further participation, and 8 patients (3%) could not be interviewed for logistic reasons.

The 58 non-participants (19%) were found to be older (69.5 versus 64 year; $t = -2.98$, $df = 288$, $P < 0.005$) and to have higher numerical fatigue scores (mean 4.7, SD 3.0) than participants (mean 3.6, SD 2.9; $t = -1.98$, $df = 263$, $P < 0.05$). No differences were found with respect to gender distribution.

Course over time

Table 3 shows the mean scores and their standard deviations for the five dimensions of fatigue and the mood component of the CES-D on each moment of assessment.

Table 2 Sample characteristics ($n = 250$)

Mean age		64 years		
Mean time since diagnosis		5.5 months		
		n	%	Range of total radiation dose, Gy[a]
Gender	Femal	103	42	
	Male	147	58	
Educational level	Less than high school	53	23	
	Lower educational level	80	34	
	High school	62	26	
	Advanced graduate degrees	41	17	
Marital status	Married	185	74	
	Living together	13	5	
	Single	22	9	
	Widowed	29	12	
Diagnosis	Head and neck	15	6	60–66
	Gastrointestinal	13	6	45–60
	Gynaecological	31	12	40–70
	Lung	26	10	50–60
	Breast	47	19	50–75
	Prostate	64	26	60–70
	Testis	7	3	26
	Other genito-urinary tract	22	9	40–70
	Haematological malignancies	18	7	40
	Miscellaneous	6	2	40–70
Karnofsky score	50	2	1	
	60	2	1	
	70	5	2	
	80	33	13	
	90	84	34	
	100	106	42	
Comorbidity		123	52	

[a] Variation in dose schemes within the tumour groups is due to variations in indications; e.g. postoperative adjuvant versus primary radiotherapeutic treatment

Table 3 Means and standard deviations for the Multidimensional Fatigue Inventory (MFI) and the mood component of the CES-D (Higher scores denote more fatigue or more depression)

Scale	T1	T2	T3
General fatigue	11.00 ± 5.70	11.68 ± 5.86	10.15 ± 5.2
Physical fatigue	11.15 ± 4.92	11.71 ± 5.25	9.77 ± 5.0
Reduced activity	11.93 ± 5.11	11.69 ± 5.25	9.67 ± 4.7
Reduced motivation	8.83 ± 4.77	8.73 ± 4.80	8.18 ± 4.6
Mental fatigue	8.30 ± 4.87	7.55 ± 4.82	6.95 ± 8.3
CES-D mood	5.25 ± 5.31	4.32 ± 4.20	3.92 ± 5.22

General fatigue increased from T1 to T2 [$t(199) = -2.54$, $P < 0.05$], and decreased from T2 to T3 [$t(146) = 3.34$, $P < 0.001$). Neither physical fatigue and reduced activity changed from T1 to T2, but both decreased from T2 to T3 [$t(146) = 4.73$, $P < 0.001$; $t(147) = 4.25$, $P < 0.001$). Reduced motivation and mental fatigue remained stable over time. Depressive mood decreased from T1 to T2 [$t(195) = 2.06$, $P < 0.05$), whereas no difference was found between T2 and T3.

Furthermore, on all three assessment moments less than 8% of the patients specifically reported their fatigue to be most intense in the morning. These patients showed relatively low depression scores on all three assessment moments (T1:4.89 ± 3.4; T2:1.67 ± 3.8; T3:2.67 ± 3.9).

Association between fatigue and depression

In Table 4 correlations between depressive mood and fatigue are shown. With some fluctuations, most of the correlations are moderate. The rather low correlation (0.21) between reduced activity and depressive mood at T1 may be considered an exception.

With respect to the prediction of fatigue by depressive mood and vice versa, results are shown in Table 5. In general, the predictive power is low in either direction. For general fatigue and physical fatigue, however, fatigue predicts depressive mood somewhat better than

Table 4 Correlations[a] between the mood component of the CES-D and the MFI scales at the three times of assessment (T1, T2, T3)

Time of assessment	T1	T2	T3
MFI	CES-D mood	CES-D mood	CES-D mood
General fatigue	0.35	0.43	0.48
Physical fatigue	0.37	0.50	0.46
Reduced activity	0.21	0.44	0.35
Reduced motivation	0.50	0.55	0.58
Reduced activity	0.51	0.41	0.33

[a] All correlations were significant at $p < 0.001$

Table 5 Prospective relations between the MFI and the mood component of the CES-D: mutual predictive power for the different time lapses

Variables:	Time lapse	Predictor:	Variance explained Fatigue	Variance explained Depressive mood
CES-D mood +		Dependent variable:	Depressive mood	Fatigue
General fatigue	T1→T2		11%	4%
	T2→T3		7%	4%
	T1→T3		8%	6%
Physical fatigue	T1→T2		11%	4%
	T2→T3		9%	9%
	T1→T3		7%	4%
Reduced activity	T1→T2		6%	1%
	T2→T3		4%	5%
	T1→T3		2%	5%
Reduced motivation	T1→T2		11%	8%
	T2→T3		11%	12%
	T1→T3		7%	19%
Mental fatigue	T1→T2		8%	7%
	T2→T3		7%	6%
	T1→T3		2%	3%

depressive mood predicts fatigue. The relatively high percentage of variance that depressive mood at T1 explains of reduced motivation at T3 is noticeable.

Association with quality of life

In Table 6 correlations between depressive mood and quality of life, and between the fatigue scale scores and quality of life are given. Remarkably, at T1 the correlations between the fatigue scales and quality of life are rather low, whereas at T2 and T3 correlations are mostly moderate. For depressive mood correlations were generally higher.

In Table 7 the results of the regression analyses of depression and fatigue on quality of life are shown. It appears that both the mood component of the CES-D and physical fatigue are important predictors of quality of life from T1 to T2, and from T2 to T3, explaining 17% and 20% of the variance, respectively. For the prediction of quality of life from T1 to T3, only the mood component of the CES-D reaches significance, explaining 10% of the variance.

Discussion

In this study we investigated whether fatigue in cancer patients undergoing radiotherapy could be considered a valid criterion for depression and the cause-and-effect relationship between these symptoms. Moreover, since the interest in these symptoms is largely determined by the assumption that they have a negative influence on patients' quality of life, we also studied this relationship. Based on the results some interesting points can be made.

If fatigue could indeed be considered a valid criterion for depression in our patients, we expected fatigue and depressive mood to follow a similar course over time. This expectation, however, was not supported by the results. Just after radiotherapy, fatigue had either remained stable or increased, depending on the dimension under investigation. Depressive mood, however, had decreased. Furthermore, 9 months after radiotherapy three of the five fatigue scales showed a decrease in fatigue, while depressive mood had remained stable.

What could explain these results? For the course of fatigue a straightforward explanation can be given. Radiotherapy is a treatment that is known to cause side effects that develop during the treatment itself and then

Table 6 Correlations[a] between the MFI, the mood component of the CES-D and quality of life (*QOL*) at the three moments of assessment (T1, T2, T3)

MFI	QOL		
	T1	T2	T3
General fatigue	−0.21	−0.46	−0.45
Physical fatigue	−0.21	−0.56	−0.47
Reduced activity	−0.16	−0.47	−0.30
Reduced motivation	−0.22	−0.48	−0.45
Mental fatigue	−0.15	−0.35	−0.29
CES-D mood	−0.51	−0.46	−0.61

[a] All correlations were significant at $p < 0.05$

mostly moderately strong relationships, showing a slight increase in strength over time. An exception was found for the mental fatigue scale. Here, a decrease in strenght of association could be seen. Remarkable was the weak relationship between reduced activity and depressive mood before radiotherapy. To conclude, this pattern of corrleations does not provide any convincing support for fatigue as a valid criterion for depression.

The last check we made on the validity of fatigue as a criterion for depression concerned the time of the day fatigue was most intense, because it has been found that many symptoms related to depression are strongest in the morning [5, 7, 26]. However, less than 8% of our patients reported that they were tired particularly in the morning. Moreover, these patients scored low on depressive mood. Thus, it seemed that the phenomenon of 'morning tiredness' was not very common in our group of patients, and if it was present it had little to do with depressive mood.

Table 7 Results of the regression analysis on quality of life for the different time lapses, using the MFI and the mood component of the CES-D scale as predictors

Time lapse	Variables included in equation	Unstandardized regression weight	T-value	*P*-value	Variance explained
T1→T2	Physical fatigue	−0.09	−3.69	0.0003	
	CES-D mood	−0.07	−3.33	0.0010	17%
T2→T3	Physical fatigue	−0.06	−1.99	0.0023	
	CES-D mood	−0.09	−3.39	0.0035	20%
T1→T3	CES-D mood	−0.10	−3.93	0.0001	10%

decline afterwards (e.g. [14]). Fatigue appears to be one of these acute side effects, reaching its peak during or just after radiotherapy and then declining [8, 9, 25]. Indeed, this course was found on the most sensitive scale of the MFI, the General Fatigue scale. However, on the other scales the initial increase did not show. This might be a consequence of the time at which the second assessment took place. On average this was 2 weeks after radiotherapy. It is conceivable that some of the acute side effects had already diminished by that time. For reduced motivation and mental fatigue another explanation can be raised in addition. On these scales all scores were quite low, suggesting that these fatigue dimensions were less relevant in our sample.

What could have been caused the decrease in depressive mood? Relief because radiotherapy is finished and side effects are already starting to diminish might be an explanation for this. Nine months later, general fatigue, physical fatigue and reduced activity had significantly decreased. This might be expected so long after treatment. Reduced motivation, mental fatigue and depressive mood, however, were still at the same level. This might be due to a bottom effect. Scores on these scales were all very low from the beginning.

The second way in which we investigated the validity of fatigue as a criterion for depression was by studing their concurrent relationship, expecting the correlations to be high and stable over time. What we found were

Next, we investigated by way of regression analyses whether there was any causal relationship between fatigue and depressive mood. Results showed that neither of these symptoms had much predictive power with respect to the other, suggesting only weak causal relationships. Some differences in predictive power between fatigue and depression can be noted, however. When considering the dimensions of general and physical fatigue, it is fatigue that induces depressive mood rather than the other way around. Moreover, a relatively large part of the variance in reduced motivation is predicted by depressive mood, while reduced motivation does not predict depressive mood to the same extent. This is a rather remarkable result, which is perfectly in line with the meaning of this particular fatigue scale. The reduced motivation scale was meant to ascertain fatigue accompanying depression [23]. Therefore, this scale can be expected to relate most strongly to depressive mood. This holds also true, although not overwhelmingly, for concurrent relations. So, although levels of depressive mood are low in this population, they induce a type of fatigue that is reflected in the reduced motivation scale.

Our third research question concerned the influence of depression and fatigue on patients' appreciation of their quality of life. Again we examined these relationships both in a concurrent and in a prospective way. The impact of fatigue was indicated by its significant and negative association with patients' quality of life. Interestingly, this association was considerably lower before treatment than at the post-treatment or follow-up assessment, suggesting that fatigue becomes more important when treatment has ended. Depressive mood showed a stronger relationship to quality of life than fatigue did. This was especially true just before radiotherapy; later, the contributions of both symptoms became more equal.

As a predictor for quality of life, depressive mood appears to be important. It remains noteworthy, however, that physical fatigue is at least as important in determining patients' quality of life as depression. To find that both psychological and physical factors contribute to quality of life is consistent with existing ideas concerning quality of life [1, 10]. It again demonstrates the importance of fatigue for these patients.

A result that arouses curiosity in our study is the finding of such low levels of depressive mood. The patients' mean scores on the total CES-D and the standard reference scores for the general population are highly comparable [3]. One explanation for this might be that we examined a relatively healthy population. Patients were treated with curative intent, which meant their prognoses were rather good. Moreover, patients who received additional treatment as a result of complications were excluded from participation. Another, even more important, explanation may be found in the way this scale was administered. In contrast to most other studies, in our study the CES-D was administered orally. This might have induced a more optimistic view of the patients' complaints because of socially desirable answering tendencies that come into play.

To conclude, the more physical aspects of fatigue, especially, were present in this population. However, they cannot be considered a valid criterion for depression. Nor do depressive mood and fatigue have a strong causal relationship. Therefore, it seems wise to be very careful in using fatigue as criterion for depression in such a population. Only for fatigue as measured with the reduced motivation scale indications are found that this might be an indicator for depression. Although depressive mood does not seem to be highly prevalent in this population, it is clearly related to perceived quality of life. In addition, physical fatigue appears to be an independent predictor of quality of life. Therefore, both psychological and physical factors should be reckomed with in this respect.

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