Chapter 4

Are anxiety and depression related to physical symptom burden?

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Submitted

Abstract

Purpose

Anxiety and depression are common symptoms in hospitalized advanced cancer patients. It is often presumed that anxiety and depression affect the occurrence and experience of physical symptoms. To analyze the relation between anxiety, depression and the presence and intensity of physical symptoms.

Patients and methods

Anxiety and depression were assessed in a hospitalized advanced cancer population (n=79) primarily by the Hospital Anxiety and Depression Scale (HADS), and also by a single-item question "Are you anxious and /or depressed?" and by the Edmonton Symptom Assessment System (ESAS). Physical symptoms were assessed by a semi-structured interview and by the ESAS.

Results

Thirty-four percent of the patients reported anxiety, 56% depression and 29% both, as assessed by the HADS. The correlations between HADS, the single-item question and the ESAS were low. No association was found between anxiety or depression and the presence of physical symptoms. Patients who were anxious or depressed had higher ESAS scores for insomnia and drowsiness; scores for pain, anorexia, asthenia, nausea and dyspnea were independent of anxiety and/or depression.

Conclusion

The relationship between anxiety, depression and the presence and intensity of physical symptoms in hospitalized advanced cancer patients is very limited.

Introduction

Anxiety and depression are frequently reported in advanced cancer patients. The prevalence of anxiety[1,2] and depression[3-5] varies considerably in different studies due to differences in patient selection and, most importantly, differences in criteria and assessment methods; overall, anxiety occurs in 23-38% and depressed mood in 40-41% of patients with incurable cancer[6]. Anxiety occurs more frequently in the first stage of cancer, while depression is more common in advanced disease[1,7]. Significant psychological distress, sometimes experienced and/or expressed as depression or anxiety, is typical for all stages of cancer. There is a lack of good data on anxiety and depression in advanced cancer patients. Anxiety has hardly been studied in these patients and the quality of the available research on depression is low due to small samples and high nonparticipation rates.[3]

To date, a variety of measuring instruments for screening and diagnosing anxiety or depression in cancer patients are used. The Hospital Anxiety and Depression Scale (HADS) and a single-item question for depression are the most widely used instruments[3,8-11].

The relation between physical symptoms and mood disorders in cancer patients is complex. Physical symptoms are used in the diagnosis and classification of mood disorders; in cancer patients such diagnostic criteria may be unreliable and of low specificity[1,12]. In clinical practice, it is often assumed that anxiety and depression affect the presence and intensity of physical symptoms and distress[7,13,14]. On the other hand, physical symptoms may lead to being depressed and/or anxious.

The main aim of this study is to analyze the relation between anxiety, depression and the presence and intensity of physical symptoms in hospitalized advanced cancer patients. To answer this research question, we first assessed anxiety and depression in this population, secondly, we compared different methods to measure anxiety and depression, and thirdly, we analyzed the influence of anxiety and depression on symptom presence and intensity.

Patients and methods

Patients

An analysis was performed of hospitalized patients with advanced cancer, who were referred to the Palliative Care Team (PCT) of the Department of Medical Oncology for symptom control from several departments of the University Medical Center Utrecht, The Netherlands. All patients had a thorough clinical assessment by one of the two clinical nurse specialists of the PCT.

Between October 1998 and March 2004, 203 patients were referred to the PCT. For 22 patients the assessment was incomplete because of cognitive impairment, mental

or physical exhaustion, or inability to understand the Dutch language. Of the remaining 181 patients, the score for the Hospital Anxiety and Depression Scale was available for 79 patients (44%). These patients represent the sample for the present analysis.

Measures

Sociodemographic and medical data were obtained from the medical and nursing files. Functional status was measured by the Karnofsky Performance Status (KPS)[15]. Symptoms were primarily assessed as a dichotomous variable (absent or present) during a semi-structured interview by the clinical nurse specialist, using a checklist[16] based on a study by the Dutch Centers for Development of Palliative Care[17]. The list includes 49 of the most frequently occurring standardized symptoms of previous prevalence studies[18-22].

Anxiety and depression were primarily assessed by means of the Hospital Anxiety and Depression Scale (HADS)[8]; the Dutch translation has been validated[23]. The HADS is a simple, sensitive, and specific screening tool for psychiatric disorders in hospitalized patients avoiding the inclusion of somatic symptoms. It consists of two scales, one for anxiety and one for depression, each including 7 items with 4 response categories. The scales of the HADS are transformed to separate scores for anxiety and depression, ranging from 0 to 20. Anxiety and depression were also assessed by means of a single-item screening question ("Are you anxious/depressed: yes or no?")[9,10] and by the Edmonton Symptom Assessment System (ESAS)[24,25]. The single-item question has been used for screening for depression in hospitalized patients. The question is related to the last week before the assessment. The original version of the ESAS uses visual analogue scales; we used a later version using a numeric scale (0-10; 0=none, 10=worst).

Patients were considered to be at risk for a mood disorder if they:

- had a score >11 on the HADS for the anxiety and/or depression scale,
- answered 'yes' to the single-item question, and/or
- had a score on the ESAS >5 or >2 for the anxiety and/or depression item. The cut-off of 5 on the ESAS was chosen as scores >5 on any numerical symptom scale from 0-10 are usually regarded as significant and indicate the need for treatment. A recent publication[26] indicated a cut-off value of 2 for anxiety and depression as a better predictor; we therefore used both cut-off values.

The intensity of some other symptoms (pain, nausea, drowsiness, anorexia, dyspnea, asthenia and insomnia) was also measured by means of the ESAS.

Analysis

Of the symptoms assessed by the checklist we analyzed only those occurring in

10% or more of the patients. The relation between anxiety, depression and the presence of physical symptoms was assessed by using chi-squared tests on the respective contingency tables. Three-dimensional contingency tables were applied to assess differences between patients who were anxious and depressed at the same time (with anxiety and depression as explanatory variables and symptoms as response variables). Statistics were calculated with 95% confidence intervals for proportions. If the validity of a standard chi-squared test was doubtful because of low frequencies, the Fischer's exact alternative for this test was used.
The Mann-Whitney test was used to compare the intensity of symptoms measured by the ESAS (pain, nausea, drowsiness, anorexia, dyspnea, asthenia and insomnia) for patients with or without anxiety and/or depression
Statistical significance was assumed if $p < .05$. Statistical analysis was done using the Statistical Package for the Social Sciences version 12.0 (SPSS Inc., Chicago, IL).

Results

Patient characteristics

Patient characteristics are summarized in Table 1. No significant differences with regard to gender, age, primary cancer site, performance status and presence of symptoms were found between the 79 patients for whom the HADS data were available and the other patients of the total sample of 181 (data not shown).
At the moment of analysis, all except five patients had died, with a median survival of 41 days (range 1-1035). Twenty-six percent of the patients died within 1 month, 57% lived for 1-6 months and 17% of the patients lived longer than 6 months after the initial consultation.
The median number of physical symptoms per patient was 4 (range 1-8). We recorded 16 physical symptoms occurring in >10% of the patients (Table 2).

Presence of anxiety and depression

Based on the HADS, anxiety occurred in 34% of the patients and depression in 56% (Table 3). When assessed by the single question, the percentages for anxiety and depression were 58% and 37%, respectively; when assessed by the ESAS, the percentages for anxiety and depression were 49% and 44%, respectively, when the cut-off of 5 was used, and 67% and 73%, respectively, with a cut-off of 2. Both anxiety and depression as measured by the HADS, single question or ESAS (with cut-off values of 5 and 2) were present simultaneously in 29%, 22% , 34% and 60% of the patients, respectively.

Table 1. Patient characteristics (n=79)

	n (%)
Gender	
Female	45 (57%)
Age (years)	
Median (range)	57 years (21-85)
Primary cancer site	
Breast	13 (16%)
Gynecological	10 (13%)
Gastrointestinal	15 (19%)
Head- and neck	8 (10%)
Lung	8 (10%)
Prostate	6 (8%)
Others	19 (24%)
Metastases	
Bone	34 (43%)
Lymph node	34 (43%)
Lung	16 (20%)
Liver	18 (22%)
Brain	5 (6%)
Karnofsky Performance Score	
30-40	33 (42%)
50-60	33 (42%)
70-80	10 (14%)
90-100	3 (4%)

Table 2. Physical symptoms present in >10% of patients

Symptom	Patients (%)
Pain	75 (95%)
Anorexia	50 (63%)
Asthenia	47 (60%)
Constipation	35 (44%)
Insomnia	35 (44%)
Nausea	29 (37%)
Vomiting	22 (28%)
Dyspnea	19 (24%)
Drowsiness	19 (24%)
Dry mouth	19 (24%)
Sore mouth	18 (23%)
Weight loss >10%	13 (17%)
Diarrhea	12 (15%)
Confusion	11 (14%)
Paralysis	11 (14%)
Pressure ulcers	8 (10%)

Comparison of the measuring instruments

As the HADS is the only validated instrument to screen for anxiety and depression

Table 3. Presence of anxiety and depression by the three measuring instruments

Anxiety	
HADS ≥11	34%
Yes[1]	58%
ESAS ≥5	49%
ESAS ≥2	67%
Depression	
HADS ≥11	56%
Yes[2]	37%
ESAS ≥5	44%
ESAS ≥2	73%
Anxiety and Depression	
HADS ≥11	29%
Yes[1,2]	22%
ESAS ≥5	34%
ESAS ≥2	60%

[1] "Are you anxious?" asked by the consulting nurse
[2] "Are you depressed?" asked by the consulting nurse

Table 4. Comparison of the instruments

	Anxiety		Depression	
HADS	<11	≥11	<11	≥11
Single item				
No	27	6	32	17
Yes	25	21	2	27
ESAS				
<5	26	2	19	11
≥5	8	19	7	17
ESAS				
<2	17	1	13	2
≥2	17	20	13	26

in physically ill patients, we considered it as the standard against which the other two instruments were compared (Table 4).

With regard to anxiety, the positive predictive value of the single-item question was 21/46 (46%) and the negative predictive value 27/33 (82%). For the ESAS (with a cut-off value of 5) the values were 19/27 (70%) and 26/28 (93%), respectively; when a cut-off value of 2 was used for the ESAS[26] the positive predictive value for anxiety was 20/37 (54%) and the negative predictive value 17/18 (94%).

Concerning depression, the positive predictive value of the single question was 27/29 (93%) and the negative predictive value 32/49 (65%). For the ESAS (with a

cut-off value of 5) the values were 17/24 (71%) and 19/30 (63%), respectively; when a cut-off of 2 was used for the ESAS26 the positive predictive value for depression was 26/39 (67%) and the negative predictive value 13/15 (87%).

Relation between anxiety, depression and symptom presence and intensity

Generally, the presence of anxiety or depression was not found to be related to symptom presence, irrespective of the assessment method used. The only exception was for the relation between anxiety (as assessed by the single question) and pain. The prevalence of pain was 96% for patients who were anxious as opposed to 80% for patients who were not anxious, based on the yes/no question (p=.001); differences were not significant if anxiety was assessed by the ESAS (p=.362) or the HADS (p=.493).

If patients with both anxiety and depression were compared with patients without either, no significant differences were found in symptom presence, except, again, for pain as assessed by the single question (p=.017).

With regard to symptom intensity, we found that patients with anxiety or depression assessed by the HADS had significantly higher ESAS-scores for insomnia and drowsiness (Table 5). There was no relationship between anxiety or depression and the ESAS-scores for pain, anorexia, asthenia, nausea and dyspnea. Results were similar when patients with both anxiety and depression were compared to patients without either (data not shown).

Table 5. Anxiety, depression and symptom intensity[1]

	Anxiety[2]			Depression[1]		
	Yes	No	p[3]	Yes	No	p[3]
Pain	5.8	6.0	.766	5.6	6.1	.410
Nausea	3.1	2.2	.159	3.0	2.0	.108
Drowsiness	4.7	3.1	.039	4.6	2.6	.009
Anorexia	6.0	6.4	.469	6.4	5.9	.737
Dyspnea	2.5	2.0	.243	2.5	1.8	.152
Asthenia	7.4	5.8	.069	7.2	5.6	.085
Insomnia	5.3	3.5	.035	4.8	3.2	.047

[1] Mean of ESAS-scores
[2] As measured with the HADS (Yes, if score ≥11; No, if score <11)
[3] Mann-Whitney test

Discussion

In a sample of hospitalized patients with far advanced cancer, we found high levels of anxiety (34%) and particularly of depression (56%), based on the scores of the HADS. These levels were high compared to the literature[2,3,5,26,27] and probably reflect the severely ill inpatient population included in our study, as demonstrated

by the high level of symptoms and the short median survival of 41 days.
We found virtually no relationship between anxiety or depression and symptom presence and only a limited relationship with symptom intensity. Therefore, symptom presence and intensity do not seem to be a reliable indicator of anxiety or depression in these patients. Conversely, anxiety and depression appear to have very limited influence on symptom presence and intensity. The lack of these relationships is contrary to what is usually assumed in clinical practice. For example, one often assumes that the presence of a symptom (e.g. pain) may induce or aggravate depression and that conversely, depression may influence the experience and intensity of that symptom.
There are several studies which look at the relation between depression and physical symptoms[2,27-31]. In contrast, studies of the relation between anxiety and physical symptoms are largely lacking.
Our study design is remarkably similar to the study of Chen et al[27] but the results are quite different. They found an increased prevalence of insomnia, pain, anorexia, fatigue and pressure sores in depressed patients (as assessed by the HADS) compared to non-depressed patients. These differences in results may be explained by patient selection; the patients in the study of Chen were mostly admitted for chemotherapy and had a mean Karnofsky score of 81%, whereas our patients were admitted for symptom control and had a mean performance score of 51%. Cultural differences (Chinese versus Dutch patients) may also have played a role. In another study, a verbal rating scale for mood was correlated with verbal rating scores for pain and fatigue[29]. However, when DSM-criteria were applied, no significant differences in symptom rating between depressed and non-depressed patients were found.
Another study looked at the relation between both depression and anxiety (assessed by the HADS) and physical symptoms in patients with advanced cancer[2]. The median Karnofsky score in this study was 60%. Multiple regression analysis showed significant associations between depression and fatigue and between anxiety and fatigue and nausea after correction for pain and illness severity.
Our data do not support the findings from these and other studies. There are some possible explanations for this discrepancy.
First, the screening instrument used may explain the results. We have used the HADS, which focuses on anhedonia and does not use any of the physical symptoms that are part of the DSM-criteria. In patients with cancer, the latter may confound diagnosis as these symptoms can result from cancer and are not indicative of depression. However, some of the studies among cancer patients have used instruments using such symptoms for diagnosing depression[32] and may thus have over diagnosed depression.

Secondly, and probably more importantly, an existing association between a symptom and depression may disappear during the course of the illness, mood having progressively decreasing influence on symptom presence and intensity as death approaches. Many studies have been performed in earlier stages of disease and in outpatient settings, while our study focused on terminally ill inpatients.

Our results showed a striking difference in prevalence of anxiety and depression depending on the instruments used. The 37% prevalence of depression resulting from the question "Are you depressed?" is lower than the 56% prevalence as assessed by the HADS and slightly higher than the 20-28% prevalence found in other studies using the same question[4,7,10,29]. Again, this may be due to patient selection. If the HADS is considered as the standard, the positive predictive value of the question (93%) is excellent, but the negative predictive value (65%) is inadequate. In other words, a patient answering 'Yes' to the question 'Are you depressed' is likely to have a high score with regard to prevalence. Lowering the on the HADS, but an answer of 'No' does not in any way exclude a high score on the HADS. For anxiety, the reverse was found. The 58% prevalence found with the single-item question was higher than the 34% prevalence based on the HADS. As far as we are aware, there are no data in the literature to compare this with. The positive predictive value (46%) of the question is inadequate, while the negative predictive value (82%) is acceptable.

Both for anxiety and depression, the ESAS items took an intermediate position cut-off value decreased the positive predictive value for anxiety, while the negative predictive value remained about the same. For depression, the positive predictive value remained the same, while the negative predictive value increased. Comparing these results to the study of Vignaroli[26] it should be noted that we used a cut-off of 5 instead of 4, which resulted in much higher positive predictive values. The optimal cut-off value remains to be determined.

In conclusion, in a sample of terminally ill hospitalized cancer patients we found high levels of anxiety and depression (as screened by means of the HADS) but no relationship with the presence of physical symptoms and only a limited relationship with symptom intensity. It is likely that such a relationship exists in earlier stages of disease, but disappears in the course of the illness supporting the concept of a common final clinical pathway in patients with advanced cancer[21]. Systematic screening for anxiety and depression is clinically relevant in advanced cancer patients admitted for symptom control. What the best screening instrument is, remains to be established[33].

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