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ORIGINAL ARTICLE

Symptom distress in advanced cancer patients with anxiety and depression in the palliative care setting

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Abstract
Background Mood disorders are among the most distressing psychiatric conditions experienced by patients with advanced cancer; however, studies have not shown a direct association of physical symptoms with depression and anxiety.
Purpose The purpose of this study is to determine the relationship between the frequency and intensity of patients' physical symptoms and their expressions of depression and anxiety.
Patients and methods We retrospectively reviewed the records of 216 patients who had participated in three previous clinical trials conducted by our group. We assessed patients' demographic data using descriptive statistics. We analyzed physical symptom frequency and intensity using the Edmonton Symptom Assessment System (ESAS) and anxiety and depression using the respective subscales of the Hospital Anxiety and Depression Scale (HADS-A and HADS-D).
Results Sixty-two percent were male; the median age was 59 years (range 20–91 years). Seventy nine (37%) of the patients had depressive mood (HADS-D≥8), and 94 (44%) had anxiety (HADS-A≥8). Patients with depressive mood expressed higher frequency of drowsiness (68/78, 64%; p=0.0002), nausea (52/79, 66%; p=0.0003), pain (74/79, 94%; p=0.0101), dyspnea (68/79, 86%; p=0.0196), worse appetite (72/79, 91%; p=0.0051), and worse well-being (78/79, 99%; p=0.0014) and expressed higher intensity of symptoms (ESAS≥1) [median (Q1–Q3)] including drowsiness [4 (3–7), p=0.0174], fatigue [7 (5–8), p<0.0001], and worse well-being [6 (5–7), p<0.0001]. Patients with anxiety expressed higher frequency of nausea (59/94, 57%; p=0.0006), pain (88/94, 89%; p=0.0031), and dyspnea (84/94, 96%, p=0.0002) and expressed a higher intensity of pain [6 (3–8), p=0.0082], fatigue [6 (5–8), p=0.0011], worse appetite [6 (4–8), p=0.005], and worse well-being [5 (3–7), p=0.0007]. Spearman's correlation showed a significant association between HADS-A and HADS-D and other symptoms in the ESAS. Spearman's correlations of HADS with ESAS-Anxiety and ESAS-Depression were 0.56 and 0.39, respectively (p<0.001).
Conclusion Expression of physical symptoms may vary in frequency and intensity among advanced cancer patients with anxiety and depression. Patients expressing high frequency and intensity of physical symptoms should be screened for mood disorders in order to provide treatment for these conditions. More research is needed.

Keywords Depression · Anxiety · Advanced cancer · Mood disorders · Symptom distress · Palliative care

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Introduction

Mood disorders are among the most frequent and devastating of all psychiatric disorders [4, 21]. Depression can coexist at a frequency of about 25% with a number of physical symptoms in patients with advanced cancer [4, 5, 12, 22, 29]. It has been documented that mood disorders in

medically ill patients are underdiagnosed and therefore undertreated [15, 23, 34, 36]. Terminally ill patients with depression may benefit from treatment even in the last weeks of life [3, 16, 20, 25, 36]. Anxiety disorders have been studied less extensively than depression, but they are thought to be relatively common among patients with cancer [35, 42]. In the palliative care setting, these disorders are common [4, 29, 42] and yet not recognized and not treated properly, causing significant distress to the patient and the family members and/or caregivers. Patients with a chronic medical illness and comorbid depression and anxiety have been compared with patients with only a chronic medical illness. The former patients have reported significantly higher numbers of medical symptoms when controlling for severity of medical disorder [13]. However, in patients receiving palliative care, the evidence is inconsistent regarding the impact of these mood disorders, physical symptoms, and quality of life. Due to these inconsistencies and with the purpose to provide evidence that supports the impact of these disorders in physical symptoms and well-being in palliative cancer patients, our study aimed to evaluate the association of the frequency and intensity of physical symptoms and well-being and depression, anxiety, and the combination of these disorders in palliative cancer patients.

Patients and methods

Prior to initiation, this study was approved by the Institutional Review Board (IRB), and an IRB waiver of consent was obtained.

We reviewed the charts of 216 patients who participated in three previous clinical trials conducted by our group. In the first of these studies, we assessed whether long-term consumption of oral opioids by men with cancer would lead to central hypogonadism and whether this hypogonadism was associated with sexual dysfunction, fatigue, anxiety, and depression. Forty-eight men underwent a number of assessments to determine the frequency of hypogonadism [30, 31]. In the second of these studies, we characterized dyspnea in 69 patients with advanced cancer who were referred to a palliative care program [32]. The third study was aimed at determining the association between spirituality and internal locus of control in 99 patients referred to a palliative care outpatient clinic for the first time (unpublished data). All patients who participated in these three studies had normal cognitive status and were able to complete a series of questionnaires lasting between 30 and 45 min.

Age, sex, and the type of cancer were recorded for each patient. The patients in these studies completed several assessment tools. From the baseline assessment tools, we collected the Edmonton Symptom Assessment System (ESAS) which was used to assess the frequency and intensity of physical symptoms and the Hospital Anxiety and Depression Scale (HADS) which was used to assess anxiety and depression (using subscales HADS-A and HADS-D, respectively).

The ESAS consists of ten items that are rated 0 to 10 (with 10 being the worst imaginable intensity of a symptom) to evaluate physical and psychological symptoms and global sense of well-being [6, 28, 33, 38]. The ESAS is easy to administer, requiring minimal effort and concentration from the patient and/or the surrogate.

The HADS tool has been validated against the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for anxiety and depression in different settings [1, 18, 19, 24]. Using the HADS-A and HADS-D subscales, the diagnoses of anxiety or depressions (respectively) are made if the patient scores 8 or higher out of 21 points in each instrument. The HADS-A has an optimal cutoff of ≥8 (sensitivity 0.89, specificity 0.75) and an area under the curve (AUC) of 0.88, and 76% of patients were correctly classified in relation to generalized anxiety disorder according to the structured interview for DSM-IV. The HADS-D has an optimal cutoff of ≥8 (sensitivity 0.80 and specificity 0.88) and an AUC of 0.93, and 87% of the patients were correctly classified in relation to major depressive episodes according to DSM-IV criteria [24].

Statistical analysis

We compared the frequency of the ESAS symptoms (score≥1) in patients with and without depressive mood (HADS-D≥8 versus <8 out of 21), patients with and without anxiety (HADS-A ≥ 8 versus <8 out of 21), and patients with or without both disorders using Chi-Square test. The intensity of the ESAS symptom scores between groups of patients with and without depressive mood and between groups of patients with and without anxiety was compared using the Wilcoxon rank-sum test.

Spearman's correlation coefficients were calculated to evaluate the association between anxiety, depressive mood, and other physical symptoms measured by ESAS and also the association between anxiety and depressive mood measured by HADS with ESAS-A and ESAS-D subscales.

We considered a significance level of <0.05 to be statistically significant.

Results

The age, sex, and primary tumor distribution for the 216 patients are summarized in Table 1 and are representative of

Table 1 Patient characteristics

Characteristics (n=216)	Frequency (%)
Median age, years (range)	59 (20–91)
Sex	
Women	82 (38)
Men	134 (62)
Race	
White	166 (76)
African American	32 (15)
Hispanic	12 (6)
Asian	5 (2)
Other	1 (1)
Cancer diagnosis	
Lung	79 (37)
Gastrointestinal	32 (15)
Genitourinary	30 (14)
Breast	18 (8)
Gynecological	12 (6)
Hematologic	11 (5)
Head and neck	10 (4)
Other	24 (11)
Total	216 (100)

the characteristics of patient referred to palliative care programs: median age, 59 years (range 20–91 years; 134 patients (62%) were male; and 166 white (76%), 32 African American (15%), and 12 Hispanic (6%). All patients had advanced cancer. Seventy-nine patients (37%) had depressive mood (HADS-D≥8). Ninety-four patients (44%) had anxiety (HADS-A≥8).

The frequency of symptoms in our population study is shown in Table 2. Patients with anxiety mood when compared with those without expressed higher frequency of nausea (59/94, 57% vs 48/122, 39%; p=0.0006), pain (88/94, 94% vs 96/121, 79%; p=0.0031), dyspnea (84/94, 89% vs 83/122, 68%; p=0.0002), and depression (79/94, 84% vs 63/122, 52%; p<0.0001), while patients with depressive mood when compared with those without it expressed higher frequency of poor appetite (72/79, 91% vs 103/136, 76%; p=0.0051), drowsiness (68/78, 87% vs 87/137, 64%; p=0.0002), nausea (52/79, 66% vs 55/137, 40%; p=0.0003), pain (74/79, 94% vs 110/136, 81%; p=0.0101), dyspnea (68/79, 86% vs 99/137, 72%; p=0.0196), worse well-being (78/79, 99% vs 117/137, 85%; p=0.0014), and anxiety (70/79, 89% vs 83/137, 61%; p<0.0001). Patients who presented both anxiety and depressive mood expressed higher frequency of multiples symptoms excepting fatigue when compared with patients without anxiety or depressive mood (Table 2).

Patients who expressed anxiety mood, when compared with those without it, expressed greater intensity of worse-appetite median [ESAS (Q1–Q3)=6 (4–8) vs 4.5 (3–6), p=0.005], fatigue [6 (5–8) vs 5 (3–7), p=0.0011], pain [6 (3–8) vs 4 (3–7), p=0.0082], worse well-being [5 (4–7) vs 5 (2–6), p=0.0007], and depression [5 (4–7) vs 3 (2–5), p<0.0001] Patients with depressive mood expressed higher intensity of drowsiness [4 (3–7) vs 4 (2–6), p=0.0175], fatigue [7 (5–8) vs 5 (3–7), p<0.0001], and worse well-being [6 (5–7) vs 4 (2–6), p<0.0001]. The patients with both mood problems showed higher intensity of multiple symptoms, especially worse well-being [6 (5–8) vs 5 (2.5–6), p<0.0001] (Table 3). Different symptoms were reported in patients with no mood disorder, those with anxiety only, those with depressive mood only, and those with both disorders.

Spearman's correlation coefficients showed significant association between HADS and ESAS-A and ESAS-D (0.56 and 0.39, respectively; p<0.001). In addition, it showed a moderate correlation (r=0.25–0.5, p<0.0001) between HADS-A and symptoms such as pain, fatigue, nausea, dyspnea, drowsiness, appetite, and well-being. Similar moderate correlation was found with HADS-D and the mentioned symptoms, excepting low correlation (r<0.25, p=0.0031) with dyspnea.

Discussion

In this study, we found that some physical symptoms are more frequently expressed in palliative care cancer patients with anxiety and/or depressive mood, although the intensity of this expression may vary considerably. Our findings suggest that patients with anxiety and/or depressive mood might sometimes express more frequently distressing symptoms with varied intensity of the same symptoms in ESAS scores (Table 2 and 3). Clinically, these findings support the importance to evaluate for presence of mood disorders in palliative care patients who express high symptom burden and difficult symptom control.

Anxiety and depression are highly prevalent in patients with advanced cancer and should be considered when evaluating these patients. Of the 216 such patients assessed in this study, 79 (37%) had depression and 94 (44%) had anxiety. The frequencies of these disorders can vary on the basis of several factors, including the assessment methods used, the setting where the study is performed, and patient selection. We used only baseline data of patients with advanced cancer who had been admitted to three clinical trials. There is no statistical difference between the frequency of anxiety and depression between these three studies. Due to the nature of our retrospective study, we did not perform structured clinical interviews according to DSM-IV to diagnose anxiety or depression, which represents a limitation of our study. Rather, we used HADS because of its accuracy as an indicator of depression and anxiety as validated in several settings against DSM-IV diagnoses [1, 18, 19, 24, 41].

Table 2 Frequency of symptoms (ESAS≥1) in advanced cancer patients with and without anxiety (HADS-A≥8 and HADS-A<8, respectively), advanced cancer patients with and without depressive mood (HADS-D≥8 and HADS-D<8, respectively), and with and without both anxiety and depression

Symptom	Patients (%) without anxiety	Patients (%) with anxiety	*p* value[a]	Patients (%) without depressive mood	Patients (%) with depressive mood	*p* value[a]	Patients (%) without anxiety or depression	Patients (%) with both anxiety and depression	*p* value[a]
Appetite	92/121 (76)	83/94 (88)	0.0219	103/136 (76)	72/79 (91)	0.0051	123/159 (77)	52/56 (93)	0.0104
Drowsiness	81/122 (66)	74/93 (80)	0.0328	87/137 (64)	68/78 (87)	0.0002	108/160 (67)	47/55 (83)	0.0104
Fatigue	115/122 (94)	91/94 (97)	0.3773	131/137 (96)	75/79 (95)	0.8178	152/156 (97)	54/56 (96)	0.6615
Nausea	48/122 (39)	59/94 (57)	0.0006	55/137 (40)	52/79 (66)	0.0003	69/160 (43)	38/56 (68)	0.0014
Pain	96/121 (79)	88/94 (94)	0.0031	110/136 (81)	74/79 (94)	0.0101	130/159 (87)	54/56 (96)	0.0072
Dyspnea	83/122 (68)	84/94 (89)	0.0002	99/137 (72)	68/79 (86)	0.0196	117/160 (73)	50/56 (89)	0.0129
Well-being	105/122 (86)	90/94 (96)	0.0173	117/137 (85)	78/79 (99)	0.0014	140/160 (87)	55/56 (98)	0.0192
Anxiety	–	–	–	83/137 (61)	70/79 (89)	<0.0001	102/160 (64)	51/56 (91)	0.0001
Depression	63/122 (52)	79/94 (84)	<0.0001	–	–	–	92/160 (58)	50/56 (89)	<0.0001

[a] Chi-square

ESAS Edmonton Symptom Assessment System, *HADS-A* Hospital Anxiety and Depression Scale: Anxiety subscale, *HADS-D* Hospital Anxiety and Depression Scale: Depression subscale

Table 3 Intensity of symptoms (ESAS≥1) in advanced cancer patients with and without anxiety (HADS-A≥8 and HADS-A<8, respectively) and with and without depressive mood (HADS-D≥8 and HADS-D<8, respectively)

Symptom	Patients without anxiety median ESAS (Q1–Q3, *n*)	Patients with anxiety median ESAS (Q1–Q3, *n*)	*p* value[a]	Patients without depressive mood median ESAS (Q1–Q3, *n*)	Patients with depressive mood Median ESAS (Q1–Q3, *n*)	*p* value*	Patients (%) without anxiety or depression median ESAS (Q1–Q3, *n*)	Patients (%) with both anxiety and depression median ESAS (Q1–Q3, *n*)	*p* value[a]
Appetite	4.5 (3–6, 92)	6 (4–8, 83)	0.0050	5 (3–7, 103)	5 (4–8, 72)	0.0656	5 (3–7, 123)	6 (4–8, 52)	0.0135
Drowsiness	4 (2–5, 81)	5 (3–7, 74)	0.0158	4 (2–6, 87)	4 (3–7, 68)	0.0175	4 (2–6, 108)	5 (3–7, 47)	0.0272
Fatigue	5 (3–7, 115)	6 (5–8, 91)	0.0011	5 (3–7, 131)	7 (5–8, 75)	<0.0001	5 (4–7, 152)	7 (5–8, 54)	0.0002
Nausea	2 (2–4.5, 48)	4 (2–6, 59)	0.0151	3 (2–5, 55)	3 (2–5, 52)	0.5867	3 (2–5, 69)	4 (2–5, 38)	0.3768
Pain	4 (3–7, 96)	6 (3–8, 88)	0.0082	5 (3–7, 110)	5 (3–8, 74)	0.0775	5 (3–7, 130)	6 (3–8, 54)	0.0683
Dyspnea	5 (3–7, 83)	5 (3–7, 84)	0.2368	5 (3–7, 99)	5 (3–7, 68)	0.7209	5 (3–7, 117)	5(3–7, 50)	0.6937
Well-being	5 (3–7, 105)	5 (3–7, 90)	0.0007	4 (2–6, 117)	6 (5–7, 78)	<0.0001	5 (2.5–6,140)	6 (5–8, 55)	<0.0001
Anxiety	–	–	–	3 (2–5, 83)	4.5 (3–7)	0.0175	3 (2–5, 102)	5 (3–7, 51)	<0.0001
Depression	3 (2–5, 63)	5 (4–7, 79)	<0.0001	–	–	–	3 (2–5, 92)	5 (3–7, 50)	0.0024

[a] Wilcoxon test

ESAS Edmonton Symptom Assessment System, *HADS-A* Hospital Anxiety and Depression Scale: Anxiety subscale, *HADS-D* Hospital Anxiety and Depression Scale: Depression subscale

The frequency of depression and anxiety as observed in our study did not vary considerably from that reported in the literature. Depression has been reported to occur in 19% patients (95% confidence interval (CI) 9–36%) and anxiety in 30% (CI 11–62%) in the last 1 to 3 weeks of life [40]. Lloyd-Williams et al (17) showed that depression is a symptom affecting approximately one in four patients receiving palliative care and that it is significantly associated with general quality of life and the presence of immobility, tiredness, and pain in this population. These data suggest that these mood disorders can persist at the end of life and/or that there could be a failure to identify depressed patients at that stage of life. In a study by Teunissen et al. [39] of hospitalized patients with advanced cancer, the frequency of depression was 56%, which is much higher than has been reported in the literature. This finding could be due to patient selection (patients where included if they were judged to be possibly anxious and/or depressed) and the setting where the study was performed (inpatient setting). Nonetheless, both anxiety and depression are highly prevalent and can coexist and cause important symptom burden to patients and more distress to caregivers.

In our study, patients with depression expressed higher intensities of fatigue, drowsiness, and worse well-being compared to those without depression, and patients with anxiety expressed higher intensities of pain, fatigue, and worse well-being. Chen and Chang [7] found that depressed cancer patients, in different stages of the disease, had a significantly greater occurrence of insomnia, pain, anorexia, fatigue, and wound or pressure sore. After controlling for the effects of pain and illness severity, Smith et al. [37] observed that, in 68 patients with advanced cancer who were under the care of palliative care services, anxiety and depression were independently associated with global health status, emotional and cognitive functioning, and fatigue. Anxiety also contributed significantly to social functioning, nausea, and vomiting.

The simultaneous presence of multiple symptoms has also been found to be predictive of depression [23, 42]. In a sample of elderly persons with cancer, a higher level of symptom severity was a significant predictor of greater depressive symptomatology [9]. Interestingly, Teunissen et al. [39], in a study of 79 hospitalized patients with advanced cancer, did not find any association between anxiety, depressed mood, and the presence and intensity of physical symptoms. Their findings differ from ours and those of other researchers [7, 15, 17, 37, 42] probably due to the differences in patient selection, the different stages of the disease and settings where the studies were performed, probably cultural differences, and most importantly an existing association between a symptom and depressed mood may disappear during the course of the illness, mood having progressively decreasing influence on symptom presence and intensity as death approaches. Drayer et al. [9], in a study of 248 elderly patients undergoing primary and psychiatric care, found that depression remained a significant predictor of somatization after controlling for age, sex, and medical comorbidities. The researchers concluded that clinicians should consider the possibility of depression in patients with multiple somatic complaints. More research is needed to better characterize the association between somatic symptom intensity and mood disorder in patients with advanced cancer.

There is no clear evidence as to why this association between physical symptoms and psychological distress exists. One possibility is that the underlying psychiatric disorder could lead to an amplification of bodily sensation and that failure to treat the symptoms effectively could lead to a secondary reactive psychiatric disorder [8, 14]. At any rate, our findings suggest that patients with consistently high frequencies and/or intensities of physical symptoms should undergo screening for potential mood disorders. Somatization is a frequent presentation of depression and occurs in patients in different settings; however, it is still associated with the underdetection of the underlying psychiatric process [2]. Whether mood disorders are a cause or consequence of symptom distress, appropriate pharmacological and nonpharmacological approaches to managing psychological distress are likely to improve symptom expression and quality of life. Other studies suggest that anxiety and depression are associated with impaired quality of life [10, 26].

Unfortunately, the limitations inherent to retrospective data review do not allow us to interpret the causal association of anxiety and depression with physical symptom intensity. In addition, there is an apparent possibility of selection bias because our sample was obtained from previous trials done by our palliative care group, although the data we collected were from the baseline evaluations only and there was no statistical difference between the frequency of anxiety and depression between the trials. Prevalence studies give associations but longitudinal studies would provide better evidence with better associations. Divergence in intensity or prevalence over time may help determine if anxiety or depression have a true association with physical symptoms. Symptom presence and intensity as an association with anxiety and/or depressed mood may disappear over time.

Implementation of screening protocols to assess for physical symptoms and mood disorders in the outpatient and inpatient settings using simple tools such as the ESAS [6, 28, 33, 38] and the distress thermometer [11, 19, 27, 36] is needed to assist in the early detection and management of both untreated physical symptoms and psychological abnormalities. ESAS in its depression and anxiety subscales

has been validated as screening tool for depression and anxiety with a cutoff of ≥2 out of 10 [41].

Future research should attempt to better characterize the association between mood disorders and symptom expression.

Conclusion

Expression of physical symptoms may vary in frequency and intensity among advanced cancer patients with anxiety and depression. A significant relationship has been observed between the presentation of anxiety and depression and the expression of some physical symptoms and well-being. Patients with consistently high expression and/or intensity of multiple symptoms should undergo screening for mood disorders so that appropriate intervention can be administered to improve the quality of life of the patients.

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