

The predictive value of symptoms for anxiety in hospice inpatients with advanced cancer

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ABSTRACT

Objective: Insight into symptoms as predictors for anxiety may help to foster early identification of anxiety and to ameliorate anxiety management. The aim of this study was to determine which frequently occurring symptoms are predictors for anxiety in advanced cancer patients recently admitted to a hospice.

Method: Symptom burden was measured in patients admitted to a hospice who died ≤ 3 month after admission using the Utrecht Symptom Diary. This is a Dutch-translated and adapted version of the Edmonton Symptom Assessment System to self-assess the 11 most prevalent symptoms and overall well-being on a 0–10 numerical rating scale. Multiple linear regression analysis was employed to analyze the predictive value of fatigue, nausea, pain, dyspnea, depressed mood, insomnia, and well-being on anxiety.

Results: A total of 211 patients were included, 42% of whom were men, and the median age was 71 years (range = 31–95). Anxiety was uncommon and rarely severe: 25% had a score ≥ 1 , and 14% had a score > 3 . After correction for age, gender, and marital status, depressed mood ($p = 0.00$) and dyspnea ($p = 0.01$) were independent predictors for anxiety and explained 23% of the variance in anxiety.

Significance of results: Hospice inpatients with advanced cancer who suffer from dyspnea and/or depressed mood are at increased risk for anxiety. Treatment of dyspnea and depressed mood may contribute to adequate anxiety management. Further research should explore other factors associated with anxiety, especially in the psychological, social, and spiritual domains.

KEYWORDS: Anxiety, Symptoms, Advanced cancer, Hospice care, Palliative care

INTRODUCTION

Anxiety is a common response to threats of uncertainty, suffering, and mortality (Traeger et al.,

2012). It is present in 18–38% of patients with incurable cancer (Kolva et al., 2011; Smith et al., 2003; Teunissen et al., 2007b). Anxiety as a symptom is prominent in cancer patients, since it is a physiological reaction that signals danger for human beings (Stiefel & Razavi, 1994). Although the clinical presentation varies from person to person, anxiety is associated with common symptoms and signs, some of

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which are related to hyperactivity of the sympathetic nervous system (Stiefel & Razavi, 1994; Wein & Amit, 2015). Younger patients are significantly more anxious than older patients, and females report more anxiety than males (Salvo et al., 2012). Furthermore, social support and belief in an afterlife are significant predictors of anxiety (Kolva et al., 2011; McClain-Jacobson et al., 2004). Furthermore, more research is available about the role of attachment styles in the prediction of anxiety: fearful-avoidant and preoccupied attachment styles significantly predict a higher level of death anxiety (Scheffold et al., 2017). Overall, anxiety is associated with poor quality of life (Latini et al., 2007; Traeger et al., 2012).

Because of its nonspecific associated symptoms, anxiety is difficult to identify and is often inadequately assessed by healthcare professionals (Ghoshal et al., 2016; Traeger et al., 2012). Insight into the symptoms that affect anxiety could help to foster early identification of anxiety and to ameliorate anxiety management.

The relation between anxiety and other symptoms is complex. From a clinical point of view, it is often assumed that the relation is bidirectional: on the one hand, anxiety affects the presence and intensity of other symptoms, while on the other hand, some other symptoms affect the presence and intensity of anxiety. In this study, we will focus on the influence of other symptoms on anxiety.

Previous studies have found a variety of symptoms in advanced cancer patients to be significantly associated with anxiety, such as fatigue (Delgado-Guay et al., 2009; Salvo et al., 2012; Smith et al., 2003; Yennurajalingam et al., 2008; 2016); nausea (Delgado-Guay et al., 2009; Salvo et al., 2012; Smith et al., 2003); pain (Delgado-Guay et al., 2009; Teunissen et al., 2007a); dyspnea (Delgado-Guay et al., 2009; Rowbottom et al., 2017; Salvo et al., 2012); depressed mood (Lasheen et al., 2009); (Delgado-Guay et al., 2009; Rhondali et al., 2012); drowsiness (Salvo et al., 2012; Teunissen et al., 2007a); insomnia (Delgado-Guay et al., 2011; Teunissen et al., 2007a); and/or overall sense of well-being (Salvo et al., 2012; Smith et al., 2003). However, these findings were inconsistent. The heterogeneity of the study populations, assessment tools, cutoff levels, and statistical methods could explain some of these inconsistencies.

No studies are available about the symptoms associated with anxiety in hospice inpatients. These associations could be different, since hospice patients are confronted with a limited life expectancy, and most of the patients included in previous studies were still receiving cancer treatment.

The aim of our study was to determine whether the symptoms found in previous studies (fatigue,

nausea, pain, dyspnea, depressed mood, and insomnia) as well as overall perceived well-being are predictors for anxiety in advanced cancer patients at admission to a hospice.

METHODS

Patients

In this cross-sectional study, we retrospectively analyzed the prospectively collected data of symptoms in advanced cancer patients admitted to a hospice in the Netherlands from June of 2007 until September of 2015. Inpatient hospice care in the Netherlands is available if patients have a life expectancy of less than 3 months. Almost all patients die in the hospice.

The study population included all adult cancer inpatients who filled out a symptom diary (the Utrecht Symptom Diary [USD]) within a week after admission. Patients who were unable or unwilling to self-assess their symptoms using the USD were excluded. In order to select a homogenous population, we included only patients who died within 3 months after admission.

Data Collection

Anxiety, fatigue, nausea, pain, dyspnea, depressed mood, insomnia, and overall well-being were assessed using the USD. The USD is an adapted and translated version of the Edmonton Symptom Assessment System (ESAS) that has been implemented in daily Dutch hospice care. It is an instrument that is employed to self-assess the 11 most prevalent symptoms and a global sense of well-being on a 0–10 numerical rating scale. A higher value implies a more severe symptom or a lower sense of well-being. Patients can add more symptoms if necessary. The USD was filled out twice a week as part of standard care to guide tailored patient care. For the analysis, we used the first USD completed by the patient within a week after admission. Baseline characteristics (including age, gender, marital status, primary diagnosis, and performance status) and duration of admission were extracted from patient files. All USD data as well as the patient and illness characteristics were entered into a database.

The data were collected anonymously. Only the database administrator could link data to individuals using a decryption key, stored separately within the database. The use of the database for research purposes was approved by the local ethics committee of the Utrecht University Medical Center (no. 11-113/C).

Data Analysis

The prevalence of symptoms was described by frequencies, dichotomizing symptom scores in the absence or presence of a symptom (scores 0 and ≥ 1 , respectively). Symptom scores greater than 3 were regarded as clinically relevant. To gain insight into potential confounders, the relationship between patient and illness characteristics and anxiety were analyzed using the Mann–Whitney or Kruskal–Wallis test. To determine the independent influence of symptoms on anxiety, a linear regression model was created with the USD anxiety score as a dependent variable and symptom scores of fatigue, nausea, pain, dyspnea, depressed mood, insomnia, and overall well-being as the independent variables. Potential confounders (gender, age, and marital status) were selected based on known relevance (Kolva et al., 2011; Salvo et al., 2012) and included in the multiple regression model. The symptoms were then added using a forward stepwise selection procedure. The final model included only statistically significant symptoms plus gender, age, and marital status as potential confounders. Assumptions of the multivariate regression analysis were checked by residuals analysis. As the distribution of the residuals was found to be skewed as a result of the many zero scores on anxiety, a logistic regression analysis was added as a sensitivity analysis to confirm the findings of the linear regression model. In this analysis, the outcome anxiety was dichotomized into no anxiety (USD anxiety score = 0), and anxiety (USD anxiety score ≥ 1).

Statistical significance (two-sided) was set at $p < 0.05$. All analyses were performed using SPSS software (v. 23, SPSS Corporation, Chicago, IL).

RESULTS

In total, 481 patients were admitted to the hospice, 211 of whom were enrolled in our study. Those patients were diagnosed with cancer, had an expected survival of < 3 months, and completed a USD during the first week of admission. In total, 88 (42%) were men, and the median age was 71 years (range = 31–95) (Table 1). The gastrointestinal tract was the most common primary cancer site. No significant differences in anxiety levels were found for gender, age, and marital status and primary cancer site. There was low to moderate correlation among the explanatory symptom variables (0.011–0.494).

Prevalence and Intensity of Selected Symptoms

Table 2 presents the prevalence and intensity scores of the selected symptoms. Anxiety was uncommon and seldom severe: only 24.6% had a score of 1 or higher, and 14.2% of patients had an anxiety score > 3 . Fatigue was the most prevalent symptom (92.4%) and was also the symptom with the highest intensity score (mean = 6.5, $SD = 2.4$).

In total, 8% of the USD anxiety scores were missing. No significant differences were found for patients with or without a missing item on the USD

Table 1. Patient characteristics ($N = 211$)

Variable		<i>n</i> (%)	Differences in anxiety levels	
Gender	Male	88 (42%)	$p = 0.77^a$	
	Female	123 (58%)		
Marital status	Married/living together	95 (45%)	$p = 0.52^a$	
	Single	115 (55%)		
Primary cancer site	Gastrointestinal	64 (30%)	$p = 0.06^b$	
	Lung	48 (23%)		
	Gynecological	24 (11%)		
	Breast	16 (8%)		
	Urological	16 (8%)		
	Other	40 (19%)		
WHO score	1	2 (1%)	$P = 0.17^b$	
	2	33 (16%)		
	3	101 (48%)		
	4	65 (31%)		
		Mean (<i>SD</i>)	Median (range)	
Age		69.6 (12.8)	71 (31–95)	$p = 0.54^{b,1}$
Admission duration in days		27.4 (21.4)	20 (1–93)	$p = 0.86^{b,2}$

^a Mann–Whitney test.

^b Kruskal–Wallis test.

¹ Divided into categories 0–40, 40–65, 65–75, 75–85, > 85 .

² Divided into categories 1, 2, and 3 months.

Table 2. Prevalence and intensity of selected symptoms ($N = 211$)

Symptoms	Mean (SD)	Median	USD score ≥ 1 n (%)	USD score >3 n (%)	Missing n (%)
Anxiety	1.2 (2.2)	0	52 (25%)	30 (14%)	17 (8%)
Fatigue	6.5 (2.4)	7	195 (92%)	181 (86%)	9 (4%)
Nausea	1.4 (2.5)	0	67 (32%)	40 (19%)	6 (3%)
Pain	2.7 (2.9)	2	123 (58%)	72 (34%)	4 (2%)
Dyspnea	2.1 (2.9)	0	87 (41%)	53 (25%)	9 (4%)
Depressed mood	1.8 (2.6)	0	76 (36%)	46 (22%)	10 (5%)
Insomnia	2.5 (3.0)	1	105 (50%)	71 (34%)	8 (4%)
Well-being	2.7 (2.4)	5	–	–	77 (37%)

anxiety score. Well-being was the item with the highest number of missing values (36.5%). Further analysis of the missing patterns showed that patients with a missing score on well-being were older than patients without a missing item on well-being. Since age was not a primary outcome, and since the Little MCAR (missing completely at random) test produced a p value of 0.925, the data were considered to be missing at random. No significant differences were found for symptom prevalence and intensity with regard to primary cancer site, with the exception of dyspnea, which was more prevalent in lung cancer patients ($p = 0.006$).

Influence of Symptoms on Anxiety

After correction for age, gender, and marital status, depressed mood ($B = 0.335$, $SE = 0.063$, $p = 0.00$) and dyspnea ($B = 0.155$, $SE = 0.059$, $p = 0.01$) were independent predictors for anxiety (Table 3). Depressed mood and dyspnea together with age, gender, and marital status explained 22.8% of the variance of anxiety.

The logistic regression analysis confirmed that patients with depressed mood ($B = 0.312$, $SE = 0.084$, $p = 0.00$) and dyspnea ($B = 0.181$, $SE = 0.074$, $p = 0.015$) had a greater chance of experiencing anx-

iety, after correction for age, gender, and marital status.

Because of the missing values, especially for well-being, the data were analyzed after multiple imputation. Depressed mood was a significant predictor for increased anxiety in 20/20 imputed datasets, and dyspnea was a significant predictor for increased anxiety in 13/20 imputed datasets. The pooled estimates for depressed mood (pooled $B = 0.0363$, $SE = 0.067$, $p = 0.00$) and dyspnea (pooled $B = 0.104$, $SE = 0.052$, $p = 0.048$) confirmed the findings of the unimputed data.

DISCUSSION

Our study was performed to obtain insight into the predictive value of fatigue, nausea, pain, dyspnea, depressed mood, and insomnia as well as overall well-being for anxiety in patients recently admitted to a hospice. In total, 75% of the patients did not express anxiety (score 0). We found that depressed mood and dyspnea were the only independent predictors for anxiety.

As in previous studies, the majority of patients reported low levels of anxiety. Hospitalized patients and patients at home had a higher prevalence and intensity of anxiety in comparison with our inpatient

Table 3. Multiple regression analysis

Covariates	B	SE	Unstandardized	
			Lower bound	Upper bound
Gender (male = 0, female = 1)	0.231	3.44	-0.449	0.911
Age	-0.013	0.013	-0.038	0.013
Marital status (married = 0, single = 1)	0.120	0.340	-0.554	0.793
Depressed mood	0.335	0.063	0.210	0.459
Dyspnea	0.155	0.059	0.037	0.273

B = indication of the contribution of each predictor to the model; $CI_{95\%}$ = 95% confidence interval; SE = standard error.

hospice sample (de Graaf et al., 2016; Salvo et al., 2012; Teunissen et al., 2007b). Differences in anxiety between hospitalized and hospice patients may be explained by the absence of uncertainty in hospice patients about the effects of cancer treatments and by their acceptance that death is inevitable. In clinical practice, specialized nurses recognized that patients at home may be more anxious due to the fact that they usually often have to cope on their own and do not have the availability of 24/7 professional care. Overall, severe anxiety appears to be more common during the early stages of a life-threatening illness.

Another explanation for the low anxiety scores is related to the meaning of the term “anxiety.” When nurses were confronted with discrepancies between the anxiety score of the patients and their own observations, patients explained their low anxiety scores by stating, “Yes, I am feeling tensed and scared sometimes, but no, I am not anxious.” It appears that patients do not always recognize themselves within the context of “anxiety.” A recent study also highlighted the concerns about the difficulty of scoring anxiety possibly resulting in underreporting of anxiety (Nekolaichuk et al., 2017).

As expected, depressed mood and dyspnea were significant predictors for increased anxiety and explain only 23% of the variance for anxiety. A similar study in advanced cancer patients receiving radiotherapy found that 16% of the variance in anxiety was explained by age, gender, nausea, drowsiness, and a global sense of well-being. Why demographic characteristics, other symptoms, and well-being were not related with anxiety in our hospice sample remains unclear and needs further exploration.

Only 23% of the variance of anxiety was explained by physical (dyspnea) and psychological (depressed mood) symptoms. Because of the limited life expectancy, anxiety in hospice patients may be predominantly related to psychological, social, and spiritual problems (Delgado-Guay et al., 2016; Parkes, 1998). Murray Parkes (1998) describes that, in addition to anxiety for worsening pain or other worsening symptoms, loss of loved ones, homes, and jobs, becoming a burden to others and losing control are the most common causes of anxiety in hospice patients, which supports this hypothesis (Parkes, 1998). Unfortunately, we have no data on psychological, social, and spiritual problems as determinants of anxiety.

As far as we know, this is the first study on anxiety in inpatient hospice patients. However, our study does have some limitations. First, the assumptions for the multiple linear regression analysis were not completely met, due to skewed residuals for almost all the symptom scores, with the exception of well-being. We therefore performed a logistic regression analysis on dichotomized anxiety scores to confirm

the findings of the linear regression analysis. Second, there is a possibility of selection bias because we selected only patients who completed a USD during the first week after admission; patients who were not able to do so were excluded. Therefore, we may have underestimated anxiety in this population. Third, we had to deal with missing values, especially for well-being, which is a common issue in palliative care research. To examine the effect of this potential bias, we analyzed the data after multiple imputations. The pooled estimates for depressed mood and dyspnea confirmed the findings of the unimputed data. Fourth, data about preexistent anxiety disorders and data about anxiolytics during admission were not available. Finally, our findings are valid only for patients who die within 3 months after admission to a hospice.

Since anxiety is a difficult symptom to observe and to treat, insight into the predictors may help health-care professionals to identify patients at risk for anxiety early on (Traeger et al., 2012).

Further research is needed to explore whether additional predictors of increased anxiety in hospice patients exist, especially with regard to the psychological, social, and spiritual dimensions. Furthermore, we need to understand the variety of predictors for anxiety along the patient’s journey, so as to develop interventions and set up an anticipatory care plan tailored to individual needs and thus increase quality of life and dying.

Meanwhile, healthcare professionals need to assess the overall symptom burden in a structured manner to monitor symptoms over time. With the knowledge that depressed mood and dyspnea are predictive symptoms for anxiety in this inpatient hospice population, healthcare professionals need to intensify monitoring for anxiety in patients who suffer from these symptoms by observing verbal and nonverbal expressions of anxiety. Assessment tools can be helpful to systematically assess symptom burden and to initiate a conversation about anxiety with the patient and/or their loved ones (Veldhuisen et al., 2016).

CONCLUSIONS

In conclusion, in this sample of hospice patients we found a relatively low level of anxiety. Depressed mood and dyspnea were significant predictors for increased anxiety. However, these symptoms, together with gender, age, and marital status, explained only 23% of the variance in anxiety. Future research should focus on different patient populations, on the complex reciprocal relationship between anxiety and other symptoms, and on the psychological, social, and spiritual problems as predictors for anxiety. In the meantime, healthcare professionals

should monitor symptom burden over time and intensify monitoring of anxiety for patients who suffer from a depressed mood and dyspnea to identify anxiety at an earlier stage and provide individual support and treatment.

DISCLOSURES

The authors hereby declare that they have no conflicts of interest to disclose.

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