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Are Anxiety and Depressive Symptoms Related to Physical Symptoms? A Prospective Study of Patients with Advanced Chronic Disease

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1. Introduction

Access to increasingly sophisticated medical care over the last century has improved the prevention and treatment of many diseases that had previously been fatal, including pneumonia, tuberculosis, acute and chronic renal failure, some cancers, and myocardial infarction. Despite these important curative advances, insufficient emphasis was initially placed on the importance of relieving symptoms and providing continuing support to patients with limited prognosis of survival. A response to this deficiency was the emergence, in the sixties, of Hospice and Palliative Care movements, which sought to improve the quality of care of terminally ill patients and their families (Saunders, 2004).

The primary goal of palliative care therapy is the optimal relief of multiple physical and psychological symptoms, with careful consideration of the spiritual and social needs of the patients and their families (Billings, 1998; WHO, 2004). To achieve optimal symptomatic relief, it is important not only to assemble a multidisciplinary team that is able to consider all aspects of the patient's situation, but also to ensure that they are able to provide coordinated and interdisciplinary therapeutic assistance to the patient. To achieve this, it is necessary that the members of the team fully understand the relationship between the myriad physical, psychological, spiritual, and social aspects of the individual and his environment.

It is sometimes assumed in clinical practice that symptoms of depression or anxiety can influence the intensity and persistence of certain physical symptoms (Vignaroli et al., 2006). Another common assumption is that physical symptoms can trigger depression or anxiety. However, these assumptions are not firmly supported by scientific data, as a number of international studies that have attempted to explore this relationship have reported contradictory results (Lloyd-Williams et al., 2004a; Chen & Chang, 2004; Teunissen et al., 2007a). There are no national studies to explain the potential link between emotional suffering and the intensity and frequency of physical symptoms other than pain.

Depressive and anxiety symptoms can reflect the existence of a psychiatric pathology. Anxiety and mood disorders occur frequently in patients with advanced chronic disease,

(Teunissen et al., 2007b; Lloyd-Williams et al., 2003; Wilson et al., 2007; Durkin et al., 2003; Meyer et al., 2003; Noorani & Montagnini, 2007) with the observed prevalence fluctuating between 17 and 46% for the former disorder, (Teunissen et al, 2007a) and between 5% and 26% in the latter (Hotopf et al., 2002). Regardless of the frequency of these disorders and their relevance to diagnosis and treatment, they are frequently under diagnosed (Vignaroli et al., 2006; Durkin et al., 2003; Palma et al., 2008; Breitbart, 1995). This low level of detection may be related to the as-yet-incomplete incorporation of mental health professionals into medical teams, as well as to insufficient medical training in the detection, assessment, and treatment of psychiatric disorders.

The Hospital Anxiety and Depression Scale (HADS) is one of the more commonly used tools to screen for anxiety and depression in hospitalized patients. Although this scale has proven to be a reliable and valid instrument for assessing anxiety and depression in patients with physical illness (Bjelland et al., 2002), its length makes it difficult to apply in terminally ill patients, who require continuing assessment of multiple additional symptoms. The Edmonton Symptom Assessment System (Bruera et al., 1991; Dudgeon et al., 1999; Chang et al., 2000) (ESAS) is a concise, valid, and internationally used tool in palliative care Chang et al., 2000), which uses self-report scales to evaluate objectively the multiple symptoms observed in this group of patients. A particular advantage of the ESAS is that it is a simple and quickly administered tool that requires very little effort and concentration from the patient. Nevertheless, the anxiety and depressive components of this scale in Spanish have not been validated for the detection of depression and anxiety.

The main goal of this study is to determine if anxiety or depressive symptoms shows a positive correlation with the intensity and frequency of physical symptoms in hospitalized patients with advanced chronic diseases. Additionally it seeks to compare the ESAS and HADS as screening tools for anxiety and depressive symptoms in this population.

2. Material and methods

This study was conducted in the internal medicine wards of the Clinical Hospital of the Pontificia Universidad Católica de Chile during seven months, and Sotero del Río Hospital during four months. It was approved by the ethics committee of both hospitals.

During the study period, 2280 patients were hospitalized in the internal medicine wards of both hospitals. Of these, 150 patients met the initial criteria for inclusion by being diagnosed with chronic disease at an advanced stage, including: (1) advanced cancer, including haematological neoplasia or solid metastasis not responding to medical treatment; (2) pulmonary obstructive lung disease with a functional class NYHA III-IV and/or requiring additional oxygen on a permanent basis; (3) chronic liver failure categorized as Child C in its basal condition; or (4) heart failure with functional class NYHA III/IV in its basal condition. The main exclusion criteria was the presence of delirium, assessed with the Confusion Assessment Method. Of this group, 124 did not present with delirium and were admitted to our study.

On each service, the patients admitted each day were evaluated according to these criteria by systematic review of their medical charts, lab tests and clinical status. Patients with no evidence of delirium were asked to sign an informed consent form. Social, demographic and

clinical data were registered: age, sex, health insurance, educational level, date of diagnosis of the underlying disease, cause of hospitalization, co-morbidities and basal Karnofsky score.

2.1 Patient assessment

We used ESAS scale to evaluate the presence and intensity of physical symptoms reported by each patient. Symptoms of anxiety and depression was evaluated using HADS and ESAS scales, both of which have been validated and translated into Spanish (Vignaroli et al., 2006; Bjelland et al., 2002; Bruera et al., 1991; Dudgeon et al., 1999; Chang et al., 2000; Herrero et al., 2003; Walker et al., 2007; Quintana et al., 2003; Tejero et al., 1986).

The ESAS scale evaluates the symptoms that occur most frequently in advanced chronic disease, including: pain, fatigue, nausea, depression, anxiety, somnolence, dyspnea, insomnia, and reduction of one's global sense of wellness. Each symptom is assessed using a self-reporting scale where 0 mean absence of symptom and 10 indicates the presence of the symptom at its maximum possible intensity. Symptoms of anxiety and depression were considered to be present when the intensity of the symptom was 1 or more. The HADS scale consists of two 7-item subscales, one for depression and one for anxiety. Each item is rated on a 4-point scale, scored from 0 to 3. In 1983, the authors of the scale, Zigmond and Snaith, proposed that a score greater than 11 indicates a clinical problem and a score from 8 to 10 indicates that the status of the symptom is uncertain, while a score of 7 or less indicates the absence of the symptom[25].

All researchers participating in the study had been previously trained in the proper application of the scales used. A separate investigator was assigned to audit the correct registration of findings in each of the cases included in the protocol. In order to avoid registration errors, two additional researchers coded and tabulated the information in an electronic database.

2.2 Statistical analysis

The numerical variables of the study were presented as mean with standard deviation, or, in a small number of cases, as the median. Categorical variables were presented as number of cases and percent. We used the nonparametric Mann-Whitney test to compare numerical variables between groups, and the chi-square or exact Fisher tests to compare percentages.

To determine the validity of the ESAS as a diagnostic test, using the HADS as the gold standard, we analyzed both sensitivity and specificity. The grade of agreement between ESAS and HADS was determined by the Kappa test. P values not greater than 0.05 were considered significant. All statistical analyses were carried out using SPSS 16.0 software.

3. Results

To evaluate the relationship between physical symptoms and symptoms of anxiety or depression, profiles of depressed and non-depressed patients and anxious and non-anxious patients were compared in terms of the number and intensity of symptoms.

Of 124 patients who met the inclusion criteria of the study, 5 were too emotionally disturbed to answer the HADS, and were excluded to receive psychological assistance. Of the remaining 119 patients, most were female (58%), with an average age of 66.9 years (range 35–95), and a mean basal Karnofsky score of 70 (range 30–100). Regarding their admission diagnosis 55 patients had cancer and 61 were diagnosed with non-oncological diseases.

Variables	N	%	Median (range)
Total participants	119	-	-
Age (years)	-	-	66.9 (35-95)
Sex (M/F) (n,%)	49 / 70	48 / 52	-
Married or communal	72	60.7	-
Single	16	13.4	-
Separated or widow	31	25.9	-
With Religion	102	85.7	-
Working	29	24.4	-
Stopped Work	28	23.5	-
Retired	56	47.1	-
Karnofsky	-	-	69.8 (30-100)
With Cancer	55	47.4	-
1. Digestive	14	25.5	-
2. Blood	11	20.0	-
3. Lung	13	10.9	-
4. Breast/Gynological	02	3.6	-
5. Other	15	27.3	-
Wihtout Cancer	61	52.6	-
1. Chronic Liver Failure Child C	17	27.9	-
2. Chronic Cardiac Failure CF IV	24	39.3	-
3. Pulmonary Obstructive Lung Disease	20	32.8	-

Table 1. Clinical characteristics and social demographics of the study cohort

We found a high prevalence of physical symptoms, fatigue being the most common (78.9%), followed by insomnia (78.7%), anorexia (76.2%), and somnolence (71.3%). At least 60% of patients reported their symptoms were of moderate to severe intensity (between 4 and 10 points on the self-report scale).

Symptoms	Frequency (%)	Mild (%)	Moderate (%)	Severe (%)
Pain	61.8	22.8	26.8	12.2
Fatigue	78.9	21.1	42.3	15.4
Nausea	17.1	8.9	5.7	2.4
Drowsiness	71.3	23.0	36.1	12.3
Dyspnea	60.7	18.0	31.1	11.5
Anorexia	76.2	18.9	30.3	27.0
Depression	68.3	26.8	24.4	17.1
Anxiety	71.3	23.8	34.4	13.1

The symptoms were catalogued as mild-moderate-severe in accordance with ESAS scoring: Mild 1-3 / Moderate: 4-7 / Severe: 8-10.

Table 2. Frequency and intensity of symptoms

According to HADS scoring, 13.6% of the patients presented with depression and 32.5% with anxiety. Using a cutoff score of 2, for ESAS, 67.5% of patients experienced anxiety and 60.2% reported depressed mood.

There was no significant difference in age, religious or marital status between patients with significant psychological distress, in the form of depression or anxiety according to HADS, and those who exhibited no psychological distress (Table III). However, significant statistical differences were found in gender, employment status and Karnofsky index. We observed that patients with psychological distress tended to be female, unemployed (87.2% of the subjects with psychological distress were not working), and having a lower basal Karnofsky index of 65, compared to 75 observed in the second group with no psychological distress (p = 0.027).

	Significant Psychological Distress*						
	Present			Absent			
	N	(%)	Median	N	(%)	Median	P
Age	-	-	63.23	-	-	66.94	.154
Men	10	25	-	39	49.4	-	.014
Women	30	75	-	40	50.6	-	
With religion	36	92.3	-	66	88	-	.477
Without religion	3	7.7	-	9	12	-	
Single	3	7.9	-	12	16.2	-	.365
With a partner	23	60.5	-	45	60.8	-	
Separate or Widow	12	31.6	-	17	23	-	
Working	5	12.8	-	24	32.4	-	.006
Not working**	34	87.2	-	50	67.6	-	
Karnofsky	-	-	65.43	-	-	74.93	.027

** Presence of depression or anxiety matching HADS store.*
*** Unemployed, not working, retire or pension*

Table 3. Analysis with respect to socio-demographic characteristics. for medical reason.

3.1 Comparison of assessment tools for depression and anxiety

Using HADS as a gold standard, ESAS was tested as a screening tool to detect depression and anxiety (Table IV). Using a cutoff score of 2 or more, we obtained a sensitivity of 87,5% for depression and 86.8% for anxiety and negative predictive values of 95.7% for depression and 86.8% for anxiety. These parameters dramatically decreased when a cutoff score of 5 was used, obtaining sensitivity of 68% for depression and 63% for anxiety.

	ESAS Depression		ESAS Anxiety	
Cutoff Point	2 (%)	5 (%)	2 (%)	5 (%)
Sensitivity	87.5	68.8	86.8	63.2
Specificity	44.1	71.6	41.8	74.7
Predictive value (+)	19.7	27.5	41.8	54.5
Predictive value (-)	95.7	93.6	86.8	80.8
Kappa	.129	.247	.224	.364
P	.016	.002	.002	.000

Table 4. Sensitivity, specificity and predictive values of the ESAS as a diagnostic test using the HADS as the gold standard

3.2 Analysis based on physical symptom profiles

Patients with anxiety had higher incidence of physical symptoms and greater severity of several symptoms compared with controls. As shown in Table V, the presence of anxiety was associated with a greater incidence of pain (p = .006), insomnia (p = .002), fatigue (p = .380), and nausea (p = .009). Likewise, as shown in Table VI, the presence of anxiety was associated with greater severity of pain (p= .001), fatigue (p= .003), anorexia (p= .022), insomnia (p= .001) and nausea (p= .009). Patients with anxiety also reported a greater loss of the sensation of global well-being (p= .004).

Patients with depression also had a higher incidence of physical symptoms and greater severity of several symptoms relative to healthy controls. As shown in Table V, depressed patients had a higher frequency of anorexia (p = .014), fatigue (p = .021), and insomnia (p = .021) than controls. These symptoms (p == .014, p = .023, p = .044, respectively), in addition to nausea (p = .017), were more severe in the depressed group (Table VI). The sensation of well-being did not differ between depressed and control individuals (p > .05).

	Frequency of Symptoms (%)					
	Anxiety			Depression		
	Yes (N:38)	No (N:80)	P	Yes (N:16)	No (N: 102)	P
Pain	78.9	52.5	.006*	81.3	57.8	.074
Fatigue	89.5	72.5	.038*	100	74.5	.021*
Nausea	28.9	10.0	.009*	37.5	12.7	.023*
Drowsy	71.1	69.6	.874	75	69.3	.774
Dyspnea	63.2	57.5	.559	62.5	58.8	.781
Anorexia	84.2	71.3	.127	100	71.6	.014*
Insomnia	94.7	70.0	.002*	100	74.5	.021*
Global Well Being	97.4	75.9	.004*	100	80.2	.070

Table 5. Frequency of symptoms: comparative analysis in patients with and without depression or anxiety

	Depression			Anxiety		
	Yes (N:16)	No (N: 102)	P	Yes (N:38)	No (N:80)	P
Pain	4.00 ± 3.25	2.66 ± 3.03	.075	4.26 ± 3.38	2.16 ± 2.69	.001*
Fatigue	5.63 ± 2.73	3.67 ± 2.99	.023*	5.18 ± 3.27	3.34 ±2.72	.003*
Nausea	1.06 ± 1.88	.51 ± 1.71	.017*	1.13 ± 2.43	.33 ± 1.21	.009*
Drowsiness	4.06 ± 3.36	3.35 ± 3.0	.427	3.87 ± 3.37	3.24 ± 2.88	.362
Dyspnea	4.06 ± 3.44	2.92 ± 3.21	.261	3.95 ± 3.71	2.66 ± 2.94	.092
Anorexia	6.50 ± 3.03	4.13 ± 3.66	.014*	5.58 ± 3.58	3.91 ± 3.60	.022*
Insomnia	6.06 ± 2.43	4.17 ± 3.54	.044*	5.92 ± 3.11	3.71 ± 3.42	.001*

(Mean± Standard Deviation of scores of the ESAS Depression and anxiety in accord with the HADS scale (≥ 11); Mann-Whitney Test)

Table 6. Presence of depression and anxiety, and intensity of physical symptoms.

4. Conclusion

The high levels of anxiety (32.5%) and depression (32.5%) we found in this study are consistent with those reported in several previous international studies of patients with advanced chronic disease (Teunissen et al., 2007a; Lloyd-Williams et al., 2003; Wilson et al., 2007; Durkin et al., 2003; Meyer et al., 2003; Noorani & Montagnini, 2007; Hotopf et al., 2002). From these results, we conclude that in patients with anxiety and depressive symptoms there is a strong association between the frequency and intensity of physical symptoms and the presence of psychological symptoms. Additionally our results suggests that the ESAS can be a useful screening tool to improve the clinical detection of anxious or depressive syndromes in terminal patients.

We found that psychological disturbance was associated with significantly more frequent and intense physical symptoms. The explanation for this correlation might be that physical symptoms play an etiologic role in triggering psychological disturbance, or, conversely, that anxiety and depression tend to increase the perceived intensity of a symptom already experienced by the patient. Although our results do not allow us to decide between these alternative theories, they do indicate that, in the presence of intense and frequent physical symptoms, the probability of finding psychological disturbance is significantly higher. This finding underlines the importance of performing a comprehensive and multidisciplinary assessment of all terminally ill patients.

Although multiple studies have sought the connection between depressed mood and physical symptoms, few have focused on the role of anxiety in this context. Chen and Chang (Chen & Chang, 2004) compared the physical symptom profiles of depressed and non-depressed patients and found, as we did, that the former group presented with a significantly larger number of symptoms. They observed a higher prevalence of insomnia, pain, anorexia, and fatigue in patients who were classified by HADS as being depressed. Our results confirm these, although, in the case of pain, the differences between depressed and non-depressed patients were not statistically significant. A study by Lloyd-Williams et al. also showed a close association between physical symptoms and depression in palliative patients (Lloyd-Williams et al., 2004a). However, the results we and others have reported lie in contrast to a Dutch report (Teunissen, 2007a). In that study, whose design was very similar to ours, no association was found between depressed or anxious mood and the presence of physical symptoms. We believe the different results may be due to cultural differences between Chilean and Dutch patients, as well as to national differences in Karnofsky score (average 65 and 50 in the Chilean and Dutch population, respectively). It should also be noted that the previous study included fewer subjects than did the current one, potentially lending less validity to their data.

The usefulness of the ESAS as a screening test in anxiety and depression is derived mainly from its sensitivity and negative predictive value. To comprehensively evaluate the usefulness of a screening test, sensitivity, specificity, and negative and positive predictive values must be evaluated. It is essential that both the sensitivity, which measures the ability of a particular tool to detect disease when it is present, and the negative predictive value, the probability that an individual with a negative test is healthy, be as higher as possible. Because a screening test is not intended to diagnose, it is less important that it has high

specificity, which measures the probability of detecting the absence of disease when there is none, because, after subjects with potential disease are identified, their assessment should always be confirmed and complemented by an adequate diagnostic procedure (in this case psychiatric interview based on DSM-IV).

When we used a cutoff score of 2, the ESAS had high sensitivity and negative predictive value for both anxiety and depression, each exceeding 86%. When the cutoff score was raised to 5, the performance dropped considerably. Thus, in agreement with the results of a previous American study (Vignaroli et al., 2006) that also used the HADS as the gold standard, our data suggests that the ideal ESAS cutoff point to achieve an acceptable level of sensitivity and specificity when screening depression and anxiety in terminal patients is 2.

Lloyd Williams et al. (2004b) found that the sensitivity and specificity of posing the simple question: are you depressed? to patients in palliative care was 74% and 55%, respectively. In addition to HADS, other tools have been designed to detect psychiatric syndromes, such as the Beck questionnaire, the Edinburgh Depression Scale, and the Schedule for Affective Disorders and Schizophrenia (SADS). However, because of their length, none of these instruments is practically applicable in clinical settings requiring daily simultaneous assessment and management of physical symptoms whose high frequency and intensity has been documented by this study and others (Chen & Chang, 2004; S Teunissen et al., 2007a; 2007b; Oi-Ling et al., 2005). For this reason, we propose ESAS as a useful and sensitive tool that can help physicians to identify, and refer to psychiatric evaluation, those patients for whom advanced disease is accompanied by symptoms of depression or anxiety.

In conclusion, in a sample of hospitalized patients with advanced chronic disease, we found that high levels of anxiety and depression were correlated with a higher frequency and intensity of physical symptoms. We found that for ESAS the ideal cutoff point to detect depressive mood and anxiety was a score of 2, which allowed ESAS to serve as a useful screening tool in this clinical context.

5. Acknowledgements

This study was supported by International Association for Hospice & Palliative Care (IAHPC).

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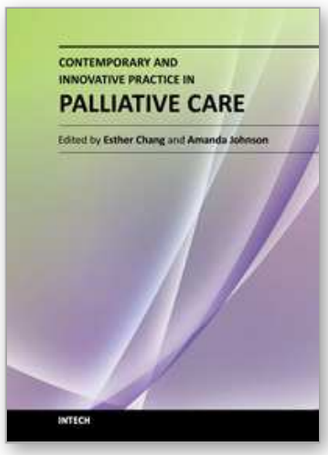

Contemporary and Innovative Practice in Palliative Care
Edited by Prof. Esther Chang

ISBN 978-953-307-986-8
Hard cover, 302 pages
Publisher InTech
Published online 10, February, 2012
Published in print edition February, 2012

This book is designed to provide a comprehensive insight unto the key and most prevalent contemporary issues associated with palliation. The reader will find viewpoints that are challenging and sometimes discerning, but at the same time motivating and thought-provoking in the care of persons requiring palliation. This book is divided into three sections. Section 1 examines contemporary practice; Section 2 looks at the challenges in practice; Section 3 discusses models of care. This book is an excellent resource for students, practising clinicians and academics. By reading the book, reflecting on the issues, challenges and opportunities ahead, we hope it will create within the reader a passion to take on, explore and further develop their palliative care practice.

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María Ignacia del Río, Alejandra Palma, Laura Tupper, Luis Villaroel, Pilar Bonati, María Margarita Reyes and Flavio Nervi (2012). Are Anxiety and Depressive Symptoms Related to Physical Symptoms? A Prospective Study of Patients with Advanced Chronic Disease, Contemporary and Innovative Practice in Palliative Care, Prof. Esther Chang (Ed.), ISBN: 978-953-307-986-8, InTech, Available from: http://www.intechopen.com/books/contemporary-and-innovative-practice-in-palliative-care/are-anxiety-and-depressive-symptoms-related-to-physical-symptoms-a-prospective-study-of-patients-wit

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