Original Article

Sleep Disturbances in Patients With Advanced Cancer in Different Palliative Care Settings

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Abstract

Context. Information regarding sleep disturbances in the population with advanced cancer is meager.

Objectives. To assess the prevalence of sleep disturbances and possible correlations with associated factors in a large number of patients with advanced cancer admitted to different palliative care settings.

Methods. This was an observational study performed in different settings of palliative care. A consecutive sample of patients with advanced cancer was prospectively assessed for a period of six months. Epidemiological and clinical data, treatments received in the last month, Karnofsky status, Edmonton Symptom Assessment System scores, and concomitant medical treatment were recorded. Patients were administered the Athens Insomnia Scale and the Hospital Anxiety and Depression Scale (HADS).

Results. A total of 820 patients were surveyed. Mean age was 69.7 years (SD 12.7), and 429 patients were males. Consistent sleep disturbances (moderate to maximum) were found in 60.8% of patients. Aged patients were less likely to have sleep disturbances, whereas a poor Karnofsky level was significantly associated with sleep problems. Breast, gastrointestinal, head and neck, lung, and prostate cancers were associated with sleep problems. Patients who had a secondary school or undergraduate education had less sleep disturbances. Hormone therapy and use of opioids and corticosteroids were positively associated with sleep disturbances, and there was a positive correlation of HADS-Anxiety and HADS-Depression scores with sleep disturbances.

Conclusion. More than 60% of palliative care patients have relevant sleep disturbances. Several factors associated with sleep disorders have been identified and should prompt physicians to make a careful examination and subsequent treatment of these disturbances. J Pain Symptom Manage 2015;50:786–792. © *2015 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words

Sleep disturbances, insomnia, palliative care, advanced cancer

Introduction

Sleep disorders have been reported to be more frequent in cancer patients than in the general population. Prevalence estimates of sleep disturbances in cancer patients vary widely, ranging from as low as 24% to as high as 95%.[1–3] Disturbances persist years after the end of treatment,[2] suggesting that sleep disturbances develop a chronic course in a substantial proportion of cancer patients.

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Sleep disturbances may involve difficulties in falling asleep, trouble staying asleep, early morning awakening, or a complaint of nonrestorative sleep with a poor corresponding sleep efficiency.[3] The methodologies that have been used to study sleep in this area have many inconsistencies and potential inadequacies. Insomnia is often perceived only as a symptom secondary to depressive or anxiety disorders with the erroneous assumption that it will resolve with adequate treatment of the underlying problem. Sleep disorders may generate a further burden of distress to patients and families, and symptoms such as depression, anxiety, pain, and fatigue tend to be exacerbated. Indeed, well-being and quality of life are dependent on the quality and quantity of sleep in both healthy and ill patients.[3,4] Sleep quality (SQ) was found to be interfering with the quality of life in 50%–75% of patients.[5,6]

Unlike other correlates of cancer, cancer-related sleep disorders have received little attention. Although insomnia is a common problem in the management of patients with cancer, sleep is inadequately assessed by primary care physicians.[4] Insomnia was found to be prevalent and under-recognized among cancer patients receiving chemotherapy.[7] Information regarding sleep disturbances in the population with advanced cancer is meager.

The Home Care-Italy group was established with the intent of disseminating and implementing the information gathered on patients with cancer followed at home and has since extended its activities to other palliative care settings for multicenter studies. The aim of this study was to assess the prevalence of sleep disturbances and possible correlations with associated factors in a large number of patients with advanced cancer admitted to different palliative care settings.

Methods

A consecutive sample of patients with advanced cancer admitted to different palliative care settings (oncology, home care, palliative care unit, or hospice) for a period of six months was prospectively assessed for this study. Informed consent was obtained. The study conforms to the principles outlined by the Declaration of Helsinki.

Inclusion criteria were a diagnosis of cancer, informed consent, and ability to provide the information requested. Exclusion criteria included cognitive problems at the time of the interview. Comatose patients, severely ill patients, or those with an immediate poor prognosis also were excluded to avoid unnecessary psychological burden.

Epidemiological and clinical data, treatments received in the last month, Karnofsky Performance Status score, education level, environment, habits, and Edmonton Symptom Assessment System (ESAS) score were recorded. Concomitant medical treatment also was recorded.

At admission to one of the palliative care services, patients were administered the Athens Insomnia Scale (AIS)[8] and the Hospital Anxiety and Depression Scale (HADS).[9] The AIS consists of eight items. The first five items assess difficulty with sleep induction, awakening during the night, early morning awakening, total sleep time, and sleep quality (SQ). The last three items pertain to the next-day consequences of insomnia, such as problems with sense of well-being, overall SQ, and sleepiness during the day. Each item of the AIS is rated on a 0–3 scale, with 0 = no problem at all and 3 = very serious problem. The total of these eight items ranges from 0 to 24, with a score of 6 or more considered to represent sleep disturbance.[10,11] The HADS comprises 14 items with two subscales: anxiety (seven items) and depression (seven items). Each item of the HADS is rated 0–3; the total score ranges from 0 to 42, with a higher score indicating more severe depression and anxiety. For this study, a total score of ≥11 was set as the cutoff for psychological distress.[12]

Statistical Analysis

We provide descriptive statistics both for categorical and continuous variables. The statistical analysis aimed at detecting factors that affect SQ according to different dimensions of the SQ issues. A preliminary explorative distributional analysis of the variables involved was performed using boxplot graphs and Shapiro-Wilk tests. An analysis of SQ and clinical predictors, adjusted by age, gender, and Karnofsky score, was carried out, testing the magnitude of each component using Wald tests. The SQ multidimensional issue was examined with linear models, adjusted for common bias sources. A χ^2 overall significance test was performed for each model used at a Type I error = 5%. The statistical analysis was performed using STATA, version 13 (StataCorp LP, College Station, TX).

Results

A total of 820 patients met the inclusion criteria and were surveyed during the study period. The mean (SD) age was 69.7 (12.7) years, and 429 patients were males. The primary tumors were, in rank order, as follows: lung, 182 (22.4%); gastrointestinal, 257 (31.6%); breast, 87 (10.7%); hematological, 75 (9.24%); urological, 35 (5.5%); gynecological, 44 (5.42%); brain, 15 (1.85%); prostate, 31 (3.8%); head and neck, 20 (2.5%); melanoma, 16 (2%); kidney, 45 (5.5%); and other 40 (5%). Recent

treatments were chemotherapy, 225 (27.7%); hormone therapy, 35 (4.3%); radiotherapy, 44 (5.4%); palliative care, 467 (57.4%); and other, 41 (5.1%). The setting of care and patient social characteristics are presented in Table 1. Current medications included, in rank order, opioids (479 patients, 59%), corticosteroids (454 patients, 56%), benzodiazepines (234 patients, 28.8%), antidepressants (90 patients, 11.1%), and neuroleptics (83 patients, 10.2%).

Most patients had consistent sleep disturbances (AIS ≥6). The distribution of patients with different degrees of sleep disturbance is shown in Fig. 1. A logistic regression was carried out using the recruitment settings as indicator variables. The odds ratio was statistically significant within this preliminary analysis (Table 2). However, the setting variable was not statistically significant when used to adjust for predictions in the models used in the main analysis. The correlations between AIS scores, primitive tumors, and other variables taken into consideration, adjusted by age and gender, are presented in Tables 3–7. Aged population was less likely to have sleep disturbances, whereas a poor Karnofsky score was significantly associated with sleep problems (Table 8). Breast, gastrointestinal, head and neck, lung, and prostate cancers were associated with sleep problems (Table 3). Patients with a secondary school or undergraduate education had less sleep disturbances (Table 4). Hormone therapy (Table 5) and the use of opioids and corticosteroids (Table 6) were positively associated with sleep disturbances. From the items of the ESAS, mild-severe anxiety was positively associated with sleep disturbances, whereas patients with mild pain, mild asthenia, and mild-to-moderate levels of well-being were less likely to have sleep disturbances (Table 7). Finally, 294 patients (39.2%) had anxiety (HADS anxiety subscale ≥11), and 399 patients (54%) had depression (HADS depression subscale ≥11). There was a positive correlation of HADS anxiety and HADS depression with sleep disturbances (Table 9).

Table 1
Setting of Care and Social Characteristics

Setting, *n* (%)	
Oncological unit	84 (10.3)
Palliative care unit	288 (35.1)
Hospice	115 (14)
Home care	333 (50.6)
Marital status, *n* (%)	
Single	63 (7.8)
Widowed	173 (21.4)
Divorced/separated	28 (3.5)
Married/cohabiting	543 (67.3)
Education, *n* (%)	
Primary	420 (51.2)
Secondary	272 (33.2)
Tertiary or undergraduate	67 (8.2)
Graduate	61 (7.4)

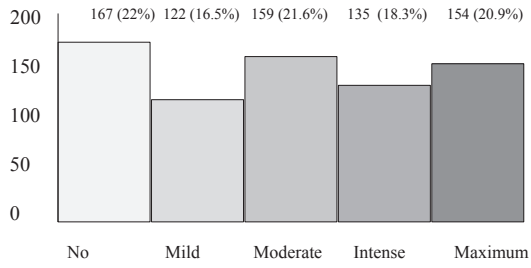

Fig. 1. Distribution of patients with different degrees of sleep disturbances.

Discussion

This cross-sectional study of patients with advanced cancer, performed in different palliative care settings, examined sleep disturbances. Sleep disorders were assessed by a validated tool (AIS) and were highly prevalent in this population. These data confirm previous observations in outpatients with advanced cancer[13] and patients on admission to a palliative care unit.[14] Several factors associated with sleep disorders have been identified.

Type of Cancer Diagnosis

The type of primary cancer has been associated with sleep disorders. The findings of this study are consistent with previous observations reported in patients with breast, lung, and head and neck cancer[6,15–17] but are in contrast with previous experience in advanced cancer patients followed at home.[18] It is likely that specific treatments, for example, hormone therapy, or disease presentation and psychophysical consequences typical of some types of cancer, may induce sleep disorders, although the reasons are not clearly understood and deserve future research.

Well-Being and Karnofsky Status

Patients with better scores of well-being were less likely to have sleep disturbances, confirming previous observations reporting that poor quality of life scores was associated with poor SQ.[5] This is confirmed by the finding that patients with lower Karnofsky scores reported more sleep disturbances.[19] A worse sense of well-being was associated with sleep disorders in

Table 2
Explorative Univariate Logistic Regression for AIS Score and Recruitment Settings

AIS[a]	OR	*P*	95% CI	
Oncological unit	12.28	0.01	1.66	90.58
Palliative care unit	3.05	0.00	1.64	5.69
Hospice	0.28	0.00	0.17	0.46
Home care	0.02	0.97	0.27	1.22

AIS = Athens Insomnia Scale; OR = odds ratio.
[a]AIS score categorized (AIS cutoff = 6).

Table 3
AIS Scores Regressed Over Primitive Tumors Adjusted by Age and Gender

AIS Score	β_i	*P*	95% CI	
Adjustment covariates				
Age	−0.06	0.001	−0.11	−0.02
Gender	−0.21	0.69	−1.21	0.81
Cancer type				
Breast	4.29	0.03	0.48	8.11
CNS	0.82	0.75	−4.26	5.91
Gastrointestinal	3.55	0.04	−0.05	7.15
Gynecological	3.19	0.12	−0.82	7.19
Head and neck	4.36	0.04	−0.09	8.80
Hematological	2.51	0.19	−1.28	6.29
Kidney	1.7	0.40	−2.29	5.69
Lung	4.93	0.008	1.29	8.57
Melanoma	Collinear			
Prostate	5.13	0.017	0.92	9.35
Others	5.48	0.009	1.40	9.56

AIS = Athens Insomnia Scale; CNS = central nervous system.
Model performance parameters: $F(12, 723) = 3.29$; $P < 0.0001$.

patients with advanced cancer.[20] Thus, patients with a poor well-being and Karnofsky scores are more likely to have sleep problems, confirming that this issue is relevant in the advanced stages of the disease.

Socioeducational Factors

Education levels had a substantial influence on sleep disturbances. This could potentially be attributed to a more likely recognition of the diagnosis and prognosis producing higher levels of anxiety and depression (see later). This aspect should be better clarified in further studies with a specific aim.

Pain, Opioids, and Hypnotics

The use of opioids was related to AIS scores. Patients with mild levels of pain were less likely to have sleep disturbances in comparison with patients with high levels of pain intensity. The relationship between pain, the use of opioids, and sleep is controversial. In a longitudinal study of women with metastatic breast cancer, high levels of pain predicted more difficulty getting to sleep and more problems of awakening during the night.[7] In a cross-sectional study of cancer outpatients, sleep disorders were significantly associated with pain intensity.[21] However, although providing opioid analgesia may improve sleep disturbances in patients with chronic pain,[22] sleep-disordered breathing has been of concern in patients receiving opioids.[23] Opioid receptors are located in the same nuclei that are active in sleep regulation, and opioids are suggested to be involved in the induction and maintenance of the sleep state.[24] Thus, the association of sleep, pain, and opioid use is quite complex and often reciprocal, as sleep disturbances themselves may impair the chronic pain process, producing a vicious circle.[25]

In patients with advanced cancer, inadequate pain control can be considered a risk factor for sleep disturbances.[20,26] In this population followed at home, the use of opioids was not associated with sleep disturbances.[6] In a similar population recruited from a single center, sleep interference was found to be different in patients receiving weak or strong opioids. It is likely that patients receiving strong opioids would

Table 4
AIS Scores Regressed Over Socioeconomic Status Adjusted by Age and Gender

AIS Score	β_i	*P*	95% CI	
Adjustment covariates				
Age	−0.07	0.001	−0.11	−0.03
Gender	−0.11	0.83	−1.09	0.88
Socioeconomic status				
Single	Collinear			
Widowed	−0.05	0.96	−2.29	2.18
Divorced/separated	0.95	0.55	−2.11	4.01
Married/cohabiting	1.78	0.25	−1.27	4.83
Primary	0.11	0.91	−1.75	1.97
Secondary	−2.36	0.01	−4.26	−0.45
Tertiary or undergraduate	−2.54	0.03	−4.94	−0.14
Degree	−5.64	0.364	−17.84	6.56

AIS = Athens Insomnia Scale.
The collinear regressors have been investigated carrying out AIS linear regressions adjusted by age and gender, getting nonstatistically significant coefficients.
Model performance parameters: $F(14, 702) = 3.22$; $P < 0.0001$.

Table 5
AIS vs. Recent Treatments Adjusted by Age and Gender

AIS	β_i	*P*	95% CI	
Adjustment covariates				
Age	−0.06	0.001	−0.10	−0.03
Gender	−0.21	0.67	−1.15	0.74
Oncological treatment				
Chemotherapy	0.96	0.41	−1.31	3.23
Hormonotherapy	3.16	0.04	0.10	6.22
Radiotherapy	0.35	0.81	−2.54	3.23
Palliative care	Collinear			
Others	0.74	0.50	−1.43	2.91

AIS = Athens Insomnia Scale.
Model performance parameters: $F(9, 704) = 2.58$; $P < 0.006$.

Table 6
AIS vs. Drugs Adjusted by Age and Gender

AIS	β_i	*P*	95% CI	
Adjustment covariates				
Age	−0.06	0.00	−0.09	−0.02
Gender	−0.42	0.36	−1.32	0.49
Drugs				
Opioids	1.78	0.00	0.83	2.73
Corticosteroids	1.92	0.00	0.95	2.88
Antidepressants	−0.80	0.29	−2.31	0.70
Neuroleptics	0.10	0.89	−1.41	1.61
Benzodiazepines	0.16	0.75	−0.86	1.18
Others	3.18	0.37	−3.84	10.19

AIS = Athens Insomnia Scale.
Model performance parameters: $F(9, 723) = 5.12$; $P < 0.0000$.

Table 7
AIS and Symptom Correlations Adjusted by Age and Gender

AIS Score	β_i	*P*	95% CI	
Adjustment covariates				
Age	−0.03	0.04	−0.06	−0.01
Gender	−0.25	0.54	−1.04	0.55
Pain				
Mild	−3.33	0.00	−4.28	−2.38
Moderate	Collinear			
Severe	−0.39	0.55	−1.69	0.90
Asthenia				
Mild	−0.98	0.12	−2.24	0.27
Moderate	Collinear			
Severe	0.56	0.27	0.44	1.57
Nausea				
Mild	−0.24	0.76	−1.81	1.33
Moderate	Collinear			
Severe	−0.69	0.46	−2.53	1.15
Anorexia				
Mild	0.79	0.12	−0.21	1.79
Moderate	Collinear			
Severe	1.02	0.05	−0.01	2.05
Anxiety				
Mild	Collinear			
Moderate	1.44	0.01	0.32	2.55
Severe	2.85	0.00	1.55	4.14
Depression				
Mild	−0.26	0.63	−1.33	0.81
Moderate	Collinear			
Severe	0.66	0.27	−0.51	1.83
Dyspnea				
Mild	−0.41	0.46	−1.52	0.69
Moderate	Collinear			
Severe	0.31	0.70	−1.29	1.91
Well-being				
Mild	−1.94	0.00	−3.36	−0.53
Moderate	−2.26	0.00	−3.29	−1.22
Severe	Collinear			

AIS = Athens Insomnia Scale.
Model performance parameters: $F(18, 716) = 15.58$; $P < 0.0000$.
The single items of the Edmonton Symptom Assessment System were grouped according to the level of intensity (0−3 = absent-mild, 4−6 = moderate, and 7−10 = severe). The values of well-being are reciprocal (the high values representing the lower well-being levels).

be in a more advanced stage of disease as quality of life and performance scores were strongly associated with poor SQ. Of interest, the level of pain partially mediated SQ.[18]

The use of hypnotics was not associated with sleep disturbances, confirming previous findings.[6] Considering the cross-sectional nature of the study, it is difficult to draw an appropriate conclusion about the influence of drugs and the indirect potential protective role of adequate pain relief.

Table 8
AIS vs. Age, Gender, and Karnofsky

AIS Score	β_i	SD_i	*P*	95% CI	
Gender	−0.39	0.46	0.39	−1.29	0.51
Age	−0.09	0.02	0.00	−0.12	−0.05
Karnofsky	−0.06	0.01	0.00	−0.09	−0.03

AIS = Athens Insomnia Scale.
Model performance parameters: $F(3, 731) = 10.06$; $P < 0.05$.

Table 9
AIS and Symptom Correlations Adjusted by Age and Gender

AIS	β_i	*P*	95% CI	
Adjustment covariates				
Age	−0.01	0.59	−0.03	0.02
Gender	−0.71	0.06	−1.38	−0.02
HADS-anxiety				
Normal	Collinear			
Borderline	2.85	0.00	1.83	3.86
Pathological	5.24	0.00	4.29	6.19
HADS-depression				
Normal	Collinear			
Borderline	2.72	0.00	1.70	3.73
Pathological	5.28	0.00	4.31	6.26

AIS = Athens Insomnia Scale; HADS = Hospital Anxiety and Depression Scale.
$F(18, 716) = 15.58$; $P < 0.0000$.
The single items of the Edmonton Symptom Assessment System were grouped according to the level of intensity (0−3 = absent-mild, 4−6 = moderate, and 7−10 = severe). The values of well-being are reciprocal (the higher values representing lower well-being).

Hormone Therapy and Corticosteroids

In the present study in a large sample of patients, the use of corticosteroids was correlated with significant changes in AIS score. Circadian disruption and sleep disorders have been found in more than 50% of patients with metastatic cancer.[27] Sleep disorders are often associated with pathological patterns of cortisol secretion, which are known to significantly inhibit the immune system.[28,29] The use of these drugs may modify the hormonal status and, as a consequence, produce sleep disturbances. In a study performed in a smaller number of patients with a short survival, the use of corticosteroids did not produce more risk for insomnia development.[18]

Psychological Factors

The finding that high levels of anxiety and depression compromise sleep was expected. Several studies have investigated this issue in cancer patients. For example, depression and stress were predictors of sleep disturbances among women with breast cancer[7] and outpatients receiving radiation therapy.[19]

Existing data in advanced cancer patients are limited. In patients with advanced cancer admitted to an acute palliative care unit, the presence of anxiety was significantly associated with less hours slept. Anxiety created more difficulties in falling asleep and produced a less restorative sleep and nightmares. Depression was associated with early awakening, nonrestorative sleep, fatigue, and nightmares.[18] Depression and anxiety, assessed by the ESAS or HADS, were associated with sleep disturbances.[6,14,26] The diagnosis of cancer, awareness of the prognosis, and the presence of other physical symptoms in such patients may influence these psychological factors.[6]

Limitations

The main limitation of this study is its cross-sectional design. However, the aim was to assess the risk of sleep disturbances at admission in different palliative care settings in a large number of patients, providing a representative population. Moreover, this is a correlation study. The results, however, should alert clinicians to this problem, enabling them to identify the more frequent risk factors that should be considered, to suggest further assessment, and possibly to find a solution; restorative sleep is fundamental in such a fragile population.

Conclusion

About 60% of patients admitted to different palliative care services have relevant sleep disturbances. Psychological profile should be assessed as well as concomitant drugs. Patients with some specific cancer diagnoses may be at higher risk for developing sleep problems. These data should prompt physicians to take into consideration direct and indirect causes that might be treated. Further longitudinal studies could provide further information about the changes in sleep disturbances along the disease trajectory and how the prevention or the treatment of some factors may play a role.

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