The Relationship of Subjective Sleep Quality, Pain, and Quality of Life in Advanced Cancer Patients

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Study Objectives: Cancer patients have been reported to complain about poor quality of sleep. This study evaluated the quality of sleep in this group, utilizing demographic data and clinical features of the cancers as assessment criteria. A secondary aim was to evaluate the correlation between the self-rated questionnaire for the quality of sleep with other instruments used in measuring pain and quality of life.

Design: A total of 102 patients with stage IV cancer completed the study and were subsequently followed for up to 10 months. Self-rated questionnaires were administered for the evaluation of quality of sleep (PSQI), quality of life Medical Outcomes Study 12-item short-form (SF-12) questionnaire, the Mental Component Summary (MSC) and the Physical Component Summary (PCS), and pain (VAS Pain). The mediation analysis model was also used to evaluate how quality of life can influence the quality of sleep through its relation to pain, the performance status of patients and analgesics (Opioids).

Patients: The mean age of the study participants was 62.8 (range: 26.0-87.0) years old. The majority (70.6%) of the patients presented with ECOG score between 2 and 3 and with metastasis (58.8%).

Results: Mean Global Sleep Quality score was 12.0±4.6. The use of the PSQI questionnaire in cancer patients demonstrated that these subjects were prone to sleep poor quality. However, the various demographic variables and clinical features of the cancers did not affect quality of sleep. Global Sleep Quality scores from the PSQI correlated with the scores obtained from the SF-12 questionnaire and with the VAS Pain results, indicating a relationship between quality of sleep, quality of life and pain. However, only the SF-12 questionnaire had predictive value on quality of sleep. Mediation analysis showed that quality of life influences quality of sleep both directly and indirectly by its effect on pain. In addition, some of the effect of quality of life on sleep quality was mediated by the use of opioids.

Conclusions: Quality of sleep in patients suffering from stage IV cancer was significantly decreased. Demographic data and clinical variables of cancers did not affect the PSQI Global Sleep Quality score. The use of the mediation model also provides evidence that quality of sleep, quality of life, pain, and opioids are strictly correlated each other.

Keywords: Quality of sleep, cancer, PSQI, SF-12, VAS pain

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INTRODUCTION

RESTORATIVE SLEEP IS IMPORTANT FOR ALL INDIVIDUALS INDEPENDENT OF SEX, RACE, AND AGE. SLEEP DISTURBANCES HAVE BEEN ASSOCIATED WITH A decline in cognitive, psychological, and physical function, as well as in an inability to take pleasure from work or social activities. This can lead to a rapid decline in quality of life with a sharp impact on one's ability to function and gain satisfaction in living.[1] There is no doubt that in clinical practice, the effects of poor quality of sleep are often more evident in patients facing serious consequences of various life-threatening illnesses than in healthy individuals. Cancer patients seem more prone to disturbed sleeping patterns such as insomnia (defined as a subjective complaint of inadequate nocturnal sleep).[2,3] Several other studies have reported that approximately half of patients with cancer suffer from sleep disturbances.[4,5]

Sleep disturbances in cancer patients may be attributable to many, varied, and complex factors such as pain, treatment side effects, and psychological causes. However, it seems that females, older individuals, and the depressed or anxious are more predisposed to sleep disturbances.[6] Other significant factors contributing to the extent of sleep difficulties may relate to the clinical features of the cancers (type, stage, and location of the cancer and/or metastasis), and the Eastern Cooperative Oncology Group (ECOG) functional capacity score. For example, lung cancer patients had higher prevalence of sleep related problems as compared to breast cancer patients. Other studies revealed that more women with breast cancer reported minor sleep difficulties than men with prostate cancer.[7-10] In addition, there is evidence that chemotherapy and radiation treatment, as well as the use of analgesic drugs, potentially elicited or aggravated sleep disruption.[11-14]

There are numerous approaches to measuring sleep, including polysomnography, actigraphy, and self-report questionnaires. To date, research on quality of sleep in cancer patients has been inadequate, as an effective measurement tool for clinical studies is lacking. There is a paucity of empirical data using psychometric measures about the prevalence and nature of sleep disturbances in cancer patients, and there is no consistent use of measures with established reliability and validity. The Pittsburgh Sleep Quality Index (PSQI) is a self-report questionnaire, commonly used to assess quality of sleep. Although it has been considered appropriate in a variety of clinical populations, it has found limited use in cancer patients.[1,15]

Disclosure Statement

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Although many clinicians agree that sleep disturbances are a common problem among cancer patients, the incidence and extent of the phenomenon has not been clearly defined. Unfortunately, there are no standard quantitative criteria to diagnose sleep disturbances in cancer patients.[16]

In order to extract useful conclusions about the quality of sleep in cancer patients, this trial evaluated subjective sleep quality in cancer patients using the psychometric properties of PSQI. This included the evaluation of the effect of the demographic and clinical characteristics (location of cancer, presence of metastasis, type of treatment), had on quality of sleep. A second objective was the investigation of the possible correlation between the PSQI questionnaire and SF-12 questionnaire, as well as the VAS Pain.

MATERIAL AND METHODS

A total of 170 eligible patients with stage IV cancer were evaluated at a palliative care unit in the Areteion Hospital of the University of Athens, Greece.

Eligibility criteria for participation included: age over 18 years, diagnosis of stage IV cancer, and an ECOG score range of 0-3. The patients had to fully comprehend and answer appropriately to the posed questions. Exclusion criteria were prior history of diagnosed psychotic illness or significant cognitive impairment. A pool of 125 patients met the inclusion criteria and were entered in the study, and from these 102 patients completed the study. The study was conducted between May 2005 and February 2006, and all patients were treated in the unit for pain relief and cancer related symptoms. Interviewers collected sociodemographic data, age, sex, education and recorded ECOG performance status scores (0-optimum performance status, 4-worst performance status).

Data regarding the site of the primary tumor, stage, metastasis, treatments and therapies used were also collected. The presence or absence of metastatic disease was determined by the classic procedures of CT scans, bone scintigraphy, and by routine histology procedures.

Treatments were recorded. Prior to admission into the study, patients were receiving numerous medications, including analgesics. These were: NSAIDs (N=99 patients), mild opioids (N=59, codeine: 120-180 mg per day), and strong opioids (N=43 patients). Of the patients receiving strong opioids, 22 received TTS Fentanyl 25 μg, and the rest (N=21) received morphine tablets, 20-60 mg per day. In spite of this medication, their pain was not controlled.

Health care professionals from the palliative care unit administered the self-report questionnaires that PSQI, SF12-PCS and SF12-MSC, and the VAS Pain for the assessment of pain intensity.

The study adhered to Good Clinical Practice and the Declaration of Helsinki, Directive 91/507/EEC. Informed consent was obtained from all patients. An approval to conduct the study was provided by the hospital's ethics committee.

Measures

Quality of sleep was assessed by means of the Greek version of PSQI, an instrument with established reliability and validity that provides evaluation of subjective sleep quality.[17] The PSQI is a self-rated questionnaire comprising 19 individual items grouped into 7 subscale scores: subjective sleep quality index, sleep latency (time needed to fall asleep), sleep duration, habitual sleep efficiency (proportion between total sleep time and time in bed), sleep disturbances (i.e., waking up during the night), use of sleeping medication, and daytime dysfunction (difficulty staying awake during daytime). Each of these subscales are weighted equally on a 0-to-3 scale to provide a Global Sleep Quality PSQI score ranging from 0 (high quality of sleep) to 21 (low quality of sleep). A score ≥5 is generally considered indicative of subjective poor sleep quality, with higher scores indicating a decline in the quality of sleep.[18] The Cronbach alpha of this measure in this study was 0.8. The PSQI questionnaire took approximately 5-10 minutes to complete.

Quality of life was measured through the SF-12.[19] It was developed to be a much shorter alternative to the Medical Outcomes Study 36-item short-form (SF-36) questionnaire so it could be used in large surveys of general and specific populations. The SF-12 is a 12-item self-administered questionnaire that yields scores for 8 areas on the quality of life. It elicits information on physical functioning (limitations in behavioral performance of everyday physical activities), role-physical functioning (extent of disability in everyday activities because of physical problems), bodily pain (severity of bodily pain and resulting limitations in activities), general health perceptions (perception of health status), vitality (energy level and fatigue), social functioning (limitations in social activities from physical or emotional problems), role-emotional (problems with work or daily activities as a result of emotional problems), mental health (psychological distress and well-being), and reported health transition. Two summary scores (each ranging from 0 to 100) are obtained: a mental component summary score (MCS) and a physical component summary score (PCS). The score to each response is added to a constant (weighted unevenly) to give a final score for that particular question. In the general population, the mean score on each component is approximately 50, with scores of 40-49 indicating mild disability, scores of 30-39 indicating moderate disability, and scores below 30 indicating severe disability in quality of life. In 14 validity tests involving physical criteria, relative validity estimates ranged from 0.43 to 0.93 (median= 0.67).[19]

The patients used the simple, self-administered VAS Pain to rate pain intensity. This instrument consists of a line numerically scaled from 0-10 (the 0-end labelled: "No pain" and the 10-end labelled: "Pain as bad as it could be"). Many studies comparing VAS Pain to numerical and/or verbal ratings have concluded that the VAS Pain (and the numerical ratings) was statistically preferable to the verbal rating scales.[20]

Statistical Analysis

Descriptive statistical methods were used to summarize recorded data. Summary statistics were presented as mean (SD), range for the continuous variables, and as frequencies for the categorical data. T-test was used to compare mean differences between groups for continuous variables at a bivariate level, while chi-square test was used for categorical variables. In order to evaluate the effect of cancer location on PSQI score, the analysis of variance (ANOVA) was performed. Bivariate relations between continuous variables were examined with Spearman product-moment correlation (r). Multiple linear regression analyses were used to predict scores on the PSQI. Mediation modeling was performed in order to explain the nature of the relation among quality of life, sleep quality,

and other variables related to the sleep quality i.e. pain, use of opioids, and ECOG score. The threshold of significance for all comparisons was 0.05. All analyses were performed using the SAS software, version 9.1.

RESULTS

A total of 102 patients were judged eligible and entered the study, with small preponderance of female subjects (54.9%). Patient demographic and clinical characteristics are summarized in Table 1. The mean age was 62.8 (range: 26-87) years old. The majority of participants (70.6%) had an ECOG functional capacity score between 2 and 3. All of them were stage IV cancer patients. Three of 5 patients had metastasis; 42.2% of the patients were receiving radiotherapy, and 42.2% were treated with strong opioids.

The mean scores of each of the 7 areas measured by the PSQI are presented in Table 2. Scoring of answers is based on a 0 to 3 scale, whereby 3 reflects poor sleep. Higher mean score was found in "sleep latency" item (2.4±0.7), followed by the "sleep duration" (2.0±1.0). The use of sleeping medication was the area in the PSQI that had the lowest mean score (0.8±1.2). The mean global sleep quality was 12.0±4.6 indicating that the participants were "poor" sleepers. Mean pain intensity was scored as 6.3±1.9 (Table 2).

Table 1—Demographic and Disease Related Patient Characteristics

	N	%
Age		
Mean 62.8 years	Range (26-87)	
Education		
Mean 8.5 years	Range (6-16)	
Sex		
Male	46	45.1
Female	56	54.9
Cancer location		
Lung	23	22.5
Breast	22	21.6
Gastrointestinal	22	21.6
Urogenital	24	23.5
Other	11	10.8
Marital status		
Married	72	70.6
Unmarried	30	29.4
ECOG score		
0-1	30	29.4
2-3	72	70.6
Stage		
IV	102	100
Metastasis		
No	42	41.2
Yes	60	58.8
Chemotherapy		
No	64	62.7
Yes	38	37.3
Radiotherapy		
No	59	57.8
Yes	43	42.2
Opioids		
Mild	59	57.8
Strong	43	42.2

Subjects with ECOG score of 2-3 (12.7±4.6) reported significantly higher levels in total PSQI when compared to the patients with ECOG score of 0-1 (10.3±4, P = 0.014). Significant difference was also observed between PSQI total and opioids; the mean of PSQI in patients taking mild opioids was 10.4 (±5) a value that was significant lower for patients taking strong opioids, (14.2±3.0, P <0.0005). Similarly, patients with metastasis reported higher scores on PSQI (12.7±4) than those without metastatic disease (11±5, P = 0.05). No other significant findings were observed in PSQI total regarding demographic and disease related characteristics (family status, sex, chemotherapy, radiotherapy, cancer location).

At the bivariate level, SF-12- MCS) (r = -0.58, P <0.0005) and (SF-12-PCS) (r = -0.29, P = 0.003) correlated with better sleep quality, while VAS Pain had a significant positive correlation (r = 0.4, P <0.0005) with PSQI total (Table 3). These results indicated that patients with low quality of life were poor quality sleepers. Furthermore, patients, who experienced intense pain had higher PSQI scores, showing that they were suffering from poor sleep quality.

Because the PSQI total was significantly correlated with VAS Pain and SF-12, further analysis was performed to examine their relationship with each PSQI component separately. All PSQI areas showed significant negative correlation with SF 12-MCS (P <0.05) (Table 4). Sleep latency and habitual sleep efficiency showed no significant correlation with SF12-PCS (P >0.05), while pain intensity was independent of the use of sleeping medication (Table 4).

At the multivariate level MCS and PCS were found to be the only significant predictors of better sleep quality, and the model explained 58% of the variability (Table 5).

The results of pain mediation of the effect of mental component quality score on quality of sleep indicated that this factor was significantly associated with the quality of sleep (R^2 = 32.7%). The Sobel test was significant (P <0.05), showing that pain partially mediated the relationship between MCS and PSQI. The mediation accounted for 13.9% of the variance of the quality of sleep score. Similarly, 33.9% of the variance in the quality of sleep score was accounted for by the mediation pathway. Pain partially mediates the relationship between PCS score and PSQI. This means that patients that with poor quality of life experience poor quality of sleep.

Table 2—Descriptive Statistics

Subscale	Mean	S.D	Min	Max
PSQI				
1. Subjective sleep quality	1.78	0.87	0	3.00
2. Sleep latency	2.39	0.71	1	3.00
3. Sleep duration	1.99	1.01	0	3.00
4. Habitual sleep efficiency	1.98	1.23	0	3.00
5. Sleep disturbances	1.39	0.51	0	2.00
6. Use of sleeping medication	0.82	1.21	0	3.00
7. Daytime dysfunction	1.64	0.82	0	3.00
Global Sleep Quality	12.00	4.55	2	19.00
SF-12				
MCS	40.09	12.04	15	60.81
PCS	31.13	9.22	16	60.25
VAS Pain				
	6.25	1.93	1	10.00

Table 3—Relationship Between PSQI Demographic and Disease-related Patients' Continuous Characteristics, SF-12 (MCS and PCS) and VAS.

	PSQI total	
	Spearman's Rho	**P-value**
Age	-0.024	0.810
Education	-0.069	0.491
MCS	-0.576	< 0.0005
PCS	-0.287	0.003
VAS Pain	0.400	< 0.0005

When the ECOG score was added in the model no mediation effect had occurred between the quality of life and the quality of sleep. More specifically, only 2.11% of the ECOG influences the direct effect of the MCS on the quality of sleep. Similarly, 14.1% of the ECOG mediates the direct effect of the PCS on the quality of sleep.

In order to clarify the relationship between the PCS and the quality of sleep, the use of opioids was entered into the model as the mediator variable, and it was shown that 30.7% of the variance in the quality of sleep score was accounted for by the mediation pathway. However, there was not any mediation effect of opioids in the relationship between MCS and PSQI (the mediation accounted for 14.4% of the variance of the quality of sleep score (PSQI).

DISCUSSION

This study yielded a mean Global Sleep Quality score of 12.00 from the PSQI questionnaire indicating that cancer patients exhibited subjective poor sleep quality (score ≥5). The high frequency of poor sleep quality in patients with cancer in the Greek population was statistically significant. Poor sleep quality must be taken into account when treating cancer patients. Additionally, the relationship between sleep quality, performance status, quality of life, and the use of opioids has not been studied fully. Two disease-related factors, ECOG performance status and the opioids used (mild versus strong), affected the responses to PSQI questionnaire as it related to Global Sleep Quality. The presence or absence of metastasis was at the cut-off of statistical significance. These findings indicate a relationship between poor sleep quality and the functional performance, mental health, and pain status of cancer patients.

Table 4—Correlation Between PSQI Components, SF-12 (MCS and PCS) and VAS Pain.

	MCS	**PCS**	**VAS**
1. Subjective sleep quality			
r	-0.449	-0.289	0.469
P-value	< 0.0005	0.003	< 0.0005
2. Sleep latency			
r	-0.372	-0.184	0.276
P-value	< 0.0005	0.064	0.005
3. Sleep duration			
r	-0.440	-0.272	0.356
P-value	< 0.0005	0.006	< 0.0005
4. Habitual sleep efficiency			
r	-0.511	-0.135	0.392
P-value	< 0.0005	0.178	< 0.0005
5. Sleep disturbances			
r	-0.263	-0.280	0.282
P-value	0.008	0.004	0.004
6. Use of sleeping medication			
r	-0.239	-0.199	-0.030
P-value	0.016	0.045	0.767
7. Daytime dysfunction			
r	-0.576	-0.214	0.393
P-value	< 0.0005	0.031	< 0.0005

Poor sleep quality was unrelated to age or sex in cancer patients, which has also been demonstrated in other studies.[21] Although many studies in the general population have consistently demonstrated that aging was a predisposing factor of insomnia, our absence of findings in this parameter suggests that the relationship between aging and sleep is more complex. It may vary as a function of several factors, such as the presence of medical conditions, including cancer. There were no indications that poor quality of sleep was related to the sex of cancer patients. Likewise, marital status, educational level, and whether the patients received radiation therapy and/or chemotherapy were not factors associated with increased risk of reporting poor sleep quality.

Opioids are often useful in initial restoration of sleep and alleviation of pain in cancer patients. However, they may actually contribute to poor sleep quality as a possible result of daytime sedation, leading to general sleepiness and alteration of circadian rhythm.[11,12] According to the PSQI results of this study, the use of strong opioids related more positively to poorer quality of sleep than mild opioids. Furthermore, the use of mediation modeling[22] also provided evidence that opioids mediated the physical component of the quality of life through quality of sleep. This is a complex issue as opioid analgesic treatment is commonly used to cope with pain. One explanation is that opioid use leads to a change in the quality of sleep, which in turn leads to a change quality of life.

Some reports have suggested that the incidence of sleep disturbances varied with cancer site and stage. In fact, some studies observed that lung cancers had poorer quality of sleep results when compared to breast cancer. Other studies conducted among

Table 5—Multiple Regression Analysis (Enter Method with All Factors) of PSQI with SF-12 (MCS and PCS), VAS, Demographic, and Clinical Variables.

Dependent: PSQI total	**B**	**S.E**	**P-value**
Constant	25.944	4.827	<0.0005
MCS	-0.239	0.033	<0.0005
PCS	-0.202	0.043	<0.0005
VAS Pain	0.045	0.209	0.830
Age	0.046	0.028	0.111
Education	0.037	0.160	0.815
Sex	0.879	0.725	0.229
Family status	-1.263	0.775	0.107
Cancer location	-0.347	0.286	0.229
ECOG	0.682	0.837	0.418
Metastasis	0.162	0.759	0.831
Chemotherapy	0.522	0.855	0.543
Radiotherapy	0.228	0.768	0.767
Opioids	0.311	0.930	0.739

R^2=0.576 F (13.88)=9.91 P < 0.0005 SE of estimate: 3.17

patients with a variety of cancer diagnoses found that breast cancer patients had the highest prevalence rate of sleep disturbances. Another study demonstrated higher prevalence in women with ovarian cancer, whereas others have reported no difference.[7,9,13] This study also demonstrated that there are no differences in quality of sleep relating to cancer site.

Recent studies in lung cancer patients have shown that subjects suffering from sleep

disturbances experienced significantly higher levels of pain and lower quality of life than those in the comparison group. It could be that sleep disturbances contributed to increased pain or that the pain interfered with sleep.[23] It has been suggested that sleep disturbances in chronic pain patients may increase pain sensitivity and create a self-perpetuating cycle of sleep disruption and increased pain.[24]

In this study, converging lines of evidence suggested that poor quality of sleep was significantly correlated to poor quality of life and pain in cancer patients, however it can not be deduced which primary factor affected the others. For example, these results did not demonstrate if quality of sleep affected quality of life, or vice versa. Additionally, only quality of life had predictive value in evaluating quality of sleep, whereas this was not the case with pain despite the documented correlation. In fact, all the subscales of the PSQI questionnaire significantly correlated to the SF 12-MCS score. There was also a significant correlation between the PSQI questionnaire and the PCS score, except for 2 of the SF 12-PSQI subscales (sleep latency and habitual sleep efficiency). VAS pain also demonstrated a significant correlation in all subscales with the exception of the use of sleeping medication. This study suggests a complex relationship between these 2 questionnaires, and therefore greater attention should be given to the association between poor sleep quality, quality of life, and pain in cancer patients. In addition, the use of mediation analysis demonstrated that patients with poor quality of life also suffered from greater pain, and poorer quality of sleep.

One important limitation of this study was that quality of sleep was assessed by a self-reporting questionnaire addressing sleep for the previous month; therefore the results could not be confirmed by polysomnographic measurements. However, the PSQI questionnaire has been widely used as a precise tool to discriminate between people with or without sleeping problems.

In conclusion, this study suggested that quality of sleep in patients suffering from stage IV cancer was significantly decreased, and as a result, these patients as a group were defined as "poor sleepers." Demographic data and clinical variables did not affect the PSQI score. However, it is possible that although the clinical presentation of the cancers did not correlate with quality of sleep, there may be other factors not assessed in this study (i.e., depression) that may influence quality of sleep in cancer patients. Furthermore, a significant correlation between the PSQI and SF-12 questionnaires, as well as the VAS Pain, was observed. However, only 2 components of SF-12 questionnaire, MCS and PCS, had predictive value on quality of sleep.

The complex interrelationships of symptoms in cancer patients need to be considered in symptom management research and practice. This study provides evidence that pain, quality of life, and quality of sleep are interrelated. The current findings could be of clinical importance, since in cancer, an initial sign of a symptom may hint the underlying cause of that symptom and, thus, indicating the need of a more effective symptom management. Clarification of the exact mechanisms by which sleep is disturbed in cancer patients represents an important area for further consideration. Continued research in larger patient groups would be beneficial in order to draw precise and reliable conclusions on the quality of sleep and also to further understand of the predicting factors to a poor quality of sleep in cancer patients. Meanwhile, considering the known relationship between sleep disturbances and quality of life (and pain) in cancer patients, it is imperative that clinicians do not underestimate these important issues and routinely assess quality of sleep. Clinicians must appreciate the often multifactorial nature of sleep disruptions in order to achieve a better and more efficacious treatment regimen. In palliative care, holistic treatment for dying patients is of great importance. Improved control of pain, through the World Health Organisation (WHO) 3-step pain relief method, and treatment of the disease related symptoms can result in marked improvement in quality of life and thereby greatly improve sleep quality.[25,26]

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