Original Article

Association Between Self-Reported Sleep Disturbance and Other Symptoms in Patients with Advanced Cancer

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Abstract

Context. Sleep disturbance (SD) is a significant source of distress for patients with cancer. Studies of patients with advanced cancer receiving palliative care to identify symptoms associated with the severity of SD are limited.

Objectives. In this study, we sought to identify the symptoms measured by the Edmonton Symptom Assessment Scale (ESAS) that are associated with SD, as measured by the Pittsburgh Sleep Quality Index (PSQI). Secondary aims of the study were to determine the association between occurrences of SD with occurrences of other symptoms and screening performance of the ESAS-Sleep item against the PSQI.

Methods. We reviewed the completed ESAS and PSQI assessments of 101 patients with advanced cancer who were receiving palliative care and had been admitted to prospective clinical trials previously initiated by us. Patients with a PSQI score of ≥5 were considered to have an SD. The frequency and severity of the ESAS symptoms items, their correlation with each other, the PSQI score, and the screening performance of the ESAS-Sleep item were calculated.

Results. The median age of patients was 60 years. Most were white non-Hispanic (73%), had lung or breast cancer (41%), and were diagnosed with SD (85%). The PSQI score was correlated with the ESAS items of pain \((r = 0.27, P = 0.006)\), dyspnea \((r = 0.25, P < 0.001)\), well-being \((r = 0.35, P < 0.0001)\), and sleep \((r = 0.44, P < 0.0001)\). Compared with patients without SD, those with SD were more likely to report pain \((P = 0.0132)\), depression \((P = 0.019)\), anxiety \((P = 0.01)\), and a poorer sense of well-being \((P = 0.035)\). An ESAS-Sleep item cutoff score of ≥3 (of 10) resulted in a sensitivity of 74% and a specificity of 73%.

Conclusion. SD is associated with increased frequency of pain, depression, anxiety, and a worse sense of well-being. These four symptoms should be assessed in all patients with advanced cancer with a complaint of SD. The ideal cutoff point...
of the ESAS-Sleep item for screening for SD is a score of $\geq 3$. More research is needed to better characterize this frequent and distressing syndrome. J Pain Symptom Manage 2011;41:819–827. Published by Elsevier Inc. on behalf of U.S. Cancer Pain Relief Committee.

**Key Words**
Sleep disorders, palliative care, advanced cancer, screening tool

### Introduction

Sleep disturbance (SD) is a significant source of distress for patients with advanced cancer. SD is experienced along the course of the illness, and it often increases during the treatment period, thus affecting a patient’s quality of life. This symptom appears to be more common among patients who are female, are older, or have mood disorders. Studies of the prevalence of SD in patients with cancer have reported values ranging from 24% to 95%. The wide range in prevalence reflects the use of different definitions of SD, assessment tools, and methodology.

According to the International Classification of Sleep Disorders and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, the diagnostic criteria of SD syndrome include difficulty with initiating sleep (more than 30 minutes to sleep onset), difficulty maintaining sleep (more than 30 minutes of nocturnal waking time), or both; the presence of sleep difficulty three nights or more per week; and sleep difficulty that causes significant impairment of daytime functioning. Stepanski et al. recently reported that 55% of patients with cancer experienced trouble sleeping, that in 26% of patients this problem was moderate or severe, and that the problem was significantly associated with fatigue, pain, and depression.

Patients who suffer from SD can experience a decline in cognitive function, an inability to engage in work or recreational activities, loss of hedonic capacity, lower quality of life, and adverse alterations to immune and neuroendocrine functions. Even so, SD is frequently underdiagnosed in clinical practice.

Few studies have assessed the severity of SD among patients receiving palliative care or identified related factors and symptoms associated with the severity of SD. In a study by Sela et al., 100 oncology outpatients who came for consultation at a multidisciplinary pain and symptom control clinic were asked and agreed to complete a self-report questionnaire that elicited information about their sleeping habits, sleep concerns, sleep enhancement strategies, and related communication with health care providers. They used a retrospective sleep questionnaire developed by the investigators, including pain, fatigue, depression, and anxiety items from the Edmonton Symptom Assessment Scale (ESAS). They found high correlations between difficulty falling asleep and fatigue ($r = 0.612$), early awakening and fatigue ($r = 0.596$), and difficulty falling asleep and anxiety ($r = 0.572$). In a study of 82 patients receiving palliative care that assessed the relationship between sleep quality, pain, psychological distress, cognitive status, and post-traumatic experience in patients with advanced cancer, post-traumatic experience and quality of life seemed to be the strongest predictors of sleep quality. In a portion of a prospective audit of 31 patients who were asked to respond to the question, “What do you think is stopping you from sleeping?” and whether pain, nausea, passing urine, dyspnea, or “do not know” was the possible cause, pain (36%) was the commonest cause of SD. This was followed by urinary frequency and dyspnea. Another prospective study evaluated the frequency and intensity of SD over seven days in 62 patients with advanced cancer and caregivers using validated assessment methods; there was no difference in objective sleep efficiency (SE), sleep fragmentation, or daytime activity comparing those patients and carers who reported that they slept well and those who reported not sleeping well. Patients who reported that they did not sleep well had significantly higher anxiety (Hospital Anxiety and Depression Scale [HADS], $P < 0.005$) and increased body pain (36-Item Short Form Health Survey body pain, $P < 0.05$).
compared with those patients who reported sleeping well, and carers who reported sleeping well were significantly less anxious (HADS, $P < 0.01$) and had less global distress (Memorial Symptom Assessment Scale [MSAS]-Global Distress Index, $P < 0.01$) and psychological symptoms (MSAS-Psychological Scale, $P < 0.001$) compared with those carers who reported not sleeping well.

The Pittsburgh Sleep Quality Index (PSQI), is one of the most validated and frequently used tools in clinical research and could be used to screen patients in the clinical setting. However, patients with advanced cancer almost always have numerous severe symptoms that need to be screened. The PSQI, and other measures of SD, also involve multiple questions, are time consuming, and thus have limited practical value in daily clinical care.

The ESAS is a commonly used tool to assess for symptoms in the clinical setting in patients with cancer. Although the ESAS consists of multiple scaled items, it is easy to administer, requires minimal effort and concentration from the patient, and can be displayed as a graph for easy viewing and interpretation. The primary aim of our study was to determine, among patients with advanced cancer, the correlation between the severity of 10 ESAS items and the PSQI global sleep score. We hypothesized that the global SD severity would be greater among patients who had more severe ESAS symptoms. Secondary aims of the study were to determine the association between occurrences of SD with occurrences of other symptoms and screening performance of the ESAS-Sleep item against the PSQI.

Materials and Methods

Study Design

In this study, we analyzed baseline data from several prospective trials previously conducted by our group (data not published). Our study was conducted between September 1, 2006, and January 31, 2008.

Prior Prospective Clinical Trials

We reviewed the data including demographic characteristics (age, sex, ethnicity, cancer type, and treatment), ESAS scores, and PSQI scores from the shadow charts of the patients enrolled in the four clinical trials designed to explore expressive writing and its effect on emotional distress (22 patients) and to investigate the use of methylphenidate and its effect on fatigue (42 patients), thalidomide and its effect on symptom cluster (21 patients), and mirtazapine and its effect on appetite (16 patients). All the trial participants had a diagnosis of advanced cancer and had been referred to the M. D. Anderson Cancer Center palliative care clinic for outpatient care. Advanced cancer is defined as a cancer that is metastatic or recurrent. The patients were aged 18 years or older and had a normal cognitive status, no preexisting major psychiatric disorder, and no severe mood disorder. In addition to other assessments required by the trials, each study participant had completed baseline ESAS and PSQI assessments. This information was used as the data set for analyses in this study. Specifically, the present study includes ESAS assessments that included SD in place of the “Other problem” items. The severity at the time of assessment of SD is rated from 0 to 10 on a numerical scale, with 0 meaning the “best sleep” and 10 meaning the “worst sleep imaginable.” This item follows the same ESAS user guidelines as the other nine symptoms on the ESAS scale. Information about demographic characteristics (age, gender, and race and ethnicity) and clinical characteristics (cancer type) was obtained from patients’ medical records.

Edmonton Symptom Assessment Scale

We designed the ESAS to assess the self-reported prevalence and severity of 10 symptoms commonly experienced by cancer patients during the previous 24 hours: pain, fatigue, nausea, depression, anxiety, drowsiness, dyspnea, loss of appetite, sense of well-being, and “other” (e.g., patient-reported SD). The severity of each symptom is rated on a numerical scale of 0–10. In a prospective study of 240 patients with a diagnosis of advanced cancer, the ESAS satisfied the criteria for internal consistency, criterion, and concurrent validity. Test-retest validity was better at two days than seven days. The overall Cronbach alpha for the ESAS instrument in this population was 0.79. It also was validated in other settings in patients with advanced cancer.
**Pittsburgh Sleep Quality Index**

The PSQI is an effective instrument with which to measure the quality and patterns of sleep. It differentiates “poor” from “good” sleep by measuring subjective sleep quality, sleep latency, sleep duration, habitual SE, SDs, use of sleeping medication, and daytime dysfunction. The original version was designed to measure sleep reports over a one-month interval. A patient indicates how frequently each item was experienced on a scale from 0 to 3. The seven component scores are then summed to obtain a global sleep score that can range from 0 to 21. A score of ≥5 indicates poor sleepers (SD). The PSQI can be used for both an initial assessment and ongoing comparative measurements across all health care settings. This self-report tool has internal consistency, as indicated by an overall reliability coefficient (Cronbach’s alpha) of 0.83. Psychometric evaluation supports its internal consistency reliability and construct validity in patients with cancer.

**Institutional Review Board Study Approval**

Each of the four prospective studies from which we gleaned data for the present study had been approved by the Institutional Review Board of The University of Texas M.D. Anderson Cancer Center. This study also was approved by this review board. Waiver of informed consent was obtained. Due diligence was taken to protect the patients’ confidentiality.

**Statistical Analysis**

We considered a patient with a PSQI global sleep score of ≥5 as having SD. The frequency and intensity of ESAS symptoms were statistically analyzed using the χ² and Wilcoxon rank-sum tests, respectively. Spearman rank correlation coefficients were used to determine the correlations among the 10 ESAS cancer-related symptom items and the PSQI global sleep score.

To determine the correlation between the severity of ESAS symptoms and the presence of SD (as indicated by a PSQI global sleep score of ≥5) in patients with advanced cancer, we compared the severity of ESAS symptoms between patients with and without SD. Given that we obtained information from 101 patients and assuming that the groups are approximately equal, we declared significant differences between these two groups as those with standard deviations ≥0.56, 80% power, and a two-sided significance level of 0.05. The detectable differences would slightly increase if the groups had unequal numbers of patients. For example, significant differences would be those with standard deviations ≥0.58 with 40 and 61 patients, ≥0.62 with 30 and 71 patients, and ≥0.94 with 10 and 91 patients.

To evaluate the association between the presence of SD (PSQI global sleep score of ≥5) and the ESAS sleep quality (ESAS-Sleep item) score, we assessed the screening performance of this ESAS-Sleep item by using the PSQI as the standard. We calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each of the different possible ESAS-Sleep item scores. Considering PSQI ≥5 as the standard for SD, the following table was constructed for each ESAS value:

<table>
<thead>
<tr>
<th>ESAS Value</th>
<th>PSQI ≥5</th>
<th>PSQI &lt;5</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive</td>
<td>False negative</td>
<td>True negative</td>
</tr>
<tr>
<td>False positive</td>
<td>True positive</td>
<td>False positive</td>
</tr>
</tbody>
</table>

The sensitivity of the ESAS-Sleep item was determined as the percentage of persons with SD determined by PSQI scores ≥5 who scored the determined ESAS-Sleep item value. This was calculated as

\[
\text{Sensitivity} = \frac{\text{True positive}}{\text{True positive + False negative}} \times 100\%
\]

The specificity of the ESAS-Sleep item was determined as the percentage of persons without SD determined by PSQI scores ≥5 who did not score the determined ESAS-Sleep item value. This was calculated as

\[
\text{Specificity} = \frac{\text{True negative}}{\text{True negative + False positive}} \times 100\%
\]

The PPV was determined as the percentage of persons having scored the determined
ESAS-Sleep item who have SDs determined by PSQI ≥5, calculated as follows:

\[
PPV = \frac{\text{True positive}}{\text{True positive} + \text{False positive}}
\]

The NPV was determined as the percentage of persons with a negative ESAS who do not have SD determined by the PSQI ≥5, calculated as follows:

\[
NPV = \frac{\text{True negative}}{\text{True negative} + \text{False negative}}
\]

**Results**

**Patient Characteristics**

The median age of the patients was 60 years (range 25–84 years). Gender was split almost evenly (Table 1). Most patients were non-Hispanic white, and the common cancer diagnoses were lung cancer (21%), breast cancer (20%), and gastrointestinal malignancies (15%). Descriptive results for the ESAS-Sleep item are depicted in Table 2.

**Table 1** Sample Characteristics (n = 101)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>53</td>
<td>52</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>74</td>
<td>73</td>
</tr>
<tr>
<td>Hispanic</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Black</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Primary cancer diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Breast</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Prostate</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Melanoma</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Hematologic</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Cancer treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy in last month</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>No treatment in last six months</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>No treatment in one month but</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>in six months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy and radiotherapy</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>combined in last month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormonal therapy in last month</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy in last month</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy in last six months</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2** Results of Sleep Assessments

<table>
<thead>
<tr>
<th>Sleep Measures</th>
<th>Mean (Standard Deviation), Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESAS-Sleep item</td>
<td>4.28 (2.88), 4</td>
</tr>
<tr>
<td>PSQI global score</td>
<td>9.56 (4.41), 9</td>
</tr>
<tr>
<td>PSQI component scores</td>
<td></td>
</tr>
<tr>
<td>Subjective sleep quality</td>
<td>1.33 (1.02), 1</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>2.54 (1.87), 2</td>
</tr>
<tr>
<td>Sleep duration</td>
<td>1.3 (1.2), 2</td>
</tr>
<tr>
<td>Habitual SE</td>
<td>66.9 (29.6), 71</td>
</tr>
<tr>
<td>SDs</td>
<td>10.4 (5.74), 6</td>
</tr>
<tr>
<td>Use of sleep medication</td>
<td>1.18 (1.5), 1</td>
</tr>
<tr>
<td>Daytime dysfunction</td>
<td>2.2 (1.83), 2</td>
</tr>
</tbody>
</table>

**Correlation Among the ESAS Items and the PSQI Global Sleep Score**

The PSQI global sleep score was significantly correlated with the ESAS items of pain (r = 0.27, P = 0.0055), dyspnea (r = 0.25, P = 0.0002), well-being (r = 0.35, P < 0.0001), and sleep (r = 0.44, P < 0.0001) (Table 3).

**Frequency and Severity of ESAS Symptoms Among Patients With or Without SD**

Eighty-six (85%) of the 101 patients were diagnosed with SD (i.e., PSQI global sleep score ≥5). Compared with patients who did not have SD (PSQI < 5), patients with SD more frequently reported pain (P = 0.013), depression (P = 0.019), and anxiety (P = 0.016) (Table 2). They also reported more severe loss of well-being (P = 0.036) (Table 4).

**Screening Performance of the ESAS-Sleep Item**

Using the PSQI global sleep score as the standard, we calculated that the screening performance of the patient-reported ESAS-Sleep item was best at a score of ≥3 (of 10). The sensitivity was 86%, specificity 53%, PPV 91%, and NPV 40% (Table 5).

**Discussion**

We found that the presence of SD in patients with advanced cancer was significantly associated with symptoms such as pain, depression, anxiety, and sense of well-being. Because of the cross-sectional nature of our study, we cannot determine whether these four symptoms are the cause, the consequence, or comorbidities of SD. Even so, because of high prevalence
of multiple symptoms in patients with advanced cancer, our findings strongly suggest that uncontrolled pain, depression, and anxiety coexist with SD and that SD should be suspected and screened as a part of routine symptom assessment.

In our study, we found associations between SD and pain, depression, anxiety, and overall well-being. Other studies in different patient populations also identified the association between SD and pain, depression, and anxiety. To our knowledge, this is the first study to look for associations of SD (as assessed by the PSQI) with all other symptoms as assessed by the ESAS. In a related prospective survey, Sela et al. found high correlations between difficulty falling asleep and fatigue ($r = 0.612$), early awakening and fatigue ($r = 0.596$), and difficulty falling asleep and anxiety ($r = 0.572$). In a study by Mystakidou et al., most (73%) patients with advanced cancer had SD; hopelessness (as assessed by the Beck Hopelessness Scale), interference of pain (Greek Brief Pain Inventory), and pain treatment (opioid use) were the factors that correlated with SD. Our findings and those of other studies support the need for research to determine the effects of aggressive management of these symptoms on the severity of SD.

At this time, there is no single-item screening tool for assessing SD in patients with advanced cancer. Further studies are needed to develop such a tool. In addition to helping screen for SD, a single-item scale would reduce patient burden, particularly when repeated assessments are necessary (such as for ratings recorded in a daily diary). Here, for the first time, we attempted to obtain data on the use of the simple question. Our preliminary findings suggest that the ideal cutoff point of the ESAS-Sleep item for the screening of SD is a score of $\leq 10$.

The data analysis of prospective studies with questionnaires (i.e., ESAS, PSQI) that were completed at one time point (baseline) limits our ability to understand how SD changes over time. Further studies are needed to support our findings. However, our results suggest that the use of the simple question to screen for SD is a feasible approach. The data analysis of prospective studies with questionnaires (i.e., ESAS, PSQI) that were completed at one time point (baseline) limits our ability to understand how SD changes over time.
especially in view of moderate correlation ($r = 0.44$) with the PSQI global score. No objective measures (e.g., polysomnography and actigraphy) or laboratory correlates (e.g., level of inflammatory cytokines) were available that could have been useful in evaluating the associations of specific types of subjective SD and objective data, such as laboratory correlates. Future prospective studies should evaluate these associations because they are important in developing biomarkers and treatments based on the particular causes of SD. Studies also should be initiated to investigate the mechanisms of SD and develop treatments based on the causation, identify risk factors for SD so as to treat it proactively in those who are at risk, and explore the role of inflammation (peripheral and central) and chronic opioid use on SD.

**Conclusion**

Among patients with advanced cancer, SD is associated with increased frequency of pain, depression, anxiety, and a worse sense of well-being. The ideal cutoff point of the ESAS-Sleep item for SD screening is $\geq 3$ of 10.

**Disclosures and Acknowledgments**

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The authors declare no conflicts of interest.

**References**


