Title page

Postprint - Title of the article: Patient-reported sleep quality in patients with advanced cancer using a WHO step III opioid for cancer pain.

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ABSTRACT

Objective Sleep is often disturbed in patients with advanced cancer. There is limited knowledge about sleep in cancer patients treated with strong opioids. This study examines sleep quality in patients with advanced cancer who are treated with a WHO step III opioid for pain.

Methods An international, multi-centre, cross-sectional study with 604 adult cancer pain patients using WHO step III opioids. Sleep quality was assessed by the Pittsburgh Sleep Quality Index (PSQI) global score (range; 0–21; score >5 indicates poor sleep). PSQI includes sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medications and daytime dysfunction. Pain and quality of life were assessed by Brief Pain Inventory and EORTC QLQ-C30 questionnaire.

Results The median age was 62 years, 42% were female, mean Karnofsky performance score (KPS) was 62.5 (±14.2) and mean oral daily morphine equivalent dose was 303 mg/24h (±543.8 mg). The mean PSQI global score was 8.8 (±4.2) (range 0-20). Seventy-eight percent were poor sleepers. All PSQI components were affected and 44% reported trouble sleeping caused by pain. In the multiple regression model predictors of PSQI global scores were pain intensity, emotional function, constipation, financial difficulties and KPS (adjusted R-Square = 0.21).

Conclusion The majority (78%) of these cancer patients treated with step III opioids experienced poor sleep quality. Pain intensity, emotional function, constipation, financial difficulties and KPS predicted poor PSQI global scores. The clinical implication is that health care personnel should routinely assess and treat sleep disturbance in patients with advanced cancer disease.

INTRODUCTION

Cancer patients experience several disease- and treatment-related symptoms. Based on a study in 3000 ambulatory cancer patients, Cleeland et al. found that disturbed sleep was one of the three most frequent symptoms.[1] The prevalence of sleep disturbance in cancer patients varies from 25 to 59 percent,[2] which is higher than the typical rate of 15-25% observed in the general population.[3]

Most studies on sleep disturbance in cancer include patients undergoing curative therapy or are conducted in cancer survivors.[4] However, sleep is recognized as a frequent concern in small samples of patients with advanced cancer with a pooled prevalence of 35% similar to shortness of breath (35%), depression (39%), and worrying (36%).[5] A Greek study including 82 patients with advanced cancer found that most patients (96%) were classified as poor sleepers by using a self-report assessment of sleep.[6] A prospective, observational UK study found that 47% of the advanced cancer patients (n=60) did not sleep well.[7] Furthermore, both an Italian and a US study observed that about 60% of palliative care patients had significant sleep disturbances.[8, 9]

Results from sleep studies in early stage of cancer may not be representative for patients with advanced cancer and short life-expectancy. Sleep in advanced cancer patients may be more influenced by symptoms such as pain, fatigue and depression, symptoms for which higher intensity is associated with a higher risk of sleep disturbance.[10] As an example, Hugel et al. found that 60% of the patients with advanced cancer reported that uncontrolled symptoms caused disturbed sleep,[11] and Delgado-Guau et al. found that sleep disturbance was associated with higher levels of pain, depression, and anxiety, and poorer well-being.[12] In semi-structured interviews with cancer patients using opioids, disturbed sleep was repeatedly reported as a bothersome consequence of having pain.[13]

Patients with advanced cancer use a high number of drugs, including opioids for moderate to severe pain.[14] Common side effects of long-term opioid use are constipation, nausea, and sedation.[15] Opioid therapy is also known to affect sleep in different ways. A clinical review from 2007 found that sleep architecture is at risk to be abnormal in patients who use opioids with reduced rapid eye movement (REM) sleep, increased wakefulness, and increased arousals from sleep, reduced total sleep time and sleep efficiency.[16] Moreover, opioids influence sleep processes, such as nocturnal apnea and O_2 desaturation.[17, 18] In patients with advanced cancer, it has been shown that the use of a World Health Organization (WHO) step III opioid was more related to poor quality of sleep than the use of the step II opioid codeine.[19] However, despite this findings, and the general knowledge about a possible effect from opioids on sleep, the relationship between opioid use and sleep is not established for cancer pain patients.

As described above, recent studies on sleep quality in advanced cancer have found an association between sleep disturbance and cancer related symptoms. However, many studies do not use an instrument designed to assess different sleep quality dimensions and include a limited number of patients. In addition, most of the studies combined patients using opioids and patients not using opioids in the analyses.[8, 20-22] Other studies have cohorts of patients treated with both WHO step II and step III opioids,[6, 23] and some studies do not report the opioid use.[7, 9, 11, 12, 24-26] Hence, the literature on sleep quality in advanced cancer consists of heterogeneous groups of patients, and the research investigating pain-related sleep disturbances in patients with advanced cancer using a WHO step III opioid is sparse. Given the potential effects from opioids on sleep and the frequent use of opioids in patients with advanced cancer, it is clinical relevant to assess sleep in this group of patients.

Therefore, the aim of the present study was to investigate sleep quality, including detailed information about sleep components, in a large cohort of patients with advanced cancer treated with a WHO step III opioid for cancer pain by addressing the following research questions: *i*: "What is the prevalence of sleep disturbance in a large international sample of cancer patients on a WHO step III opioid?" ii: "To what extent do pain intensity and other prevalent symptoms correlate with sleep quality in this cohort? *iii*: "To what extent is pain intensity and other cancer variables related to sleep quality in this cohort?"

METHODS

This study is a sub-study of the European Pharmacogenetic Opioid Study (EPOS), an international multicentre, cross-sectional study.[14] Within the EPOS study, nine hospitals in Denmark, Germany, Lithuania, Norway and Switzerland, prospectively recruited patients for self-reports of sleep quality. Adult patients (>18 years) with a malignant disease and a treatment with a WHO step III opioid for cancer pain were included.[27] Patients not consenting to participate in the study or not competent in the language used at the study centre were excluded from the study. The study was approved by ethical committees at each study centre and performed according to the rules of the Declaration of Helsinki. Written informed consent was obtained from all patients before inclusion.

Patient reported outcome measures

Sleep quality was reported by the modified Pittsburgh Sleep Quality Index (PSQI).[28] The PSQI assesses sleep quality during the previous month and consists of 19 self-rated questions. The 19 items are grouped into seven component scores, weighted equally on a 0-3 scale. The components are subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications and daytime dysfunction.[28] The seven component scores are summed to yield a PSQI global score denoting sleep quality, with a range of 0-21; higher scores indicate worse sleep quality. PSQI global scores > 5 indicate poor sleep.[12, 28]

Patients scored their pain intensity on the Brief Pain Inventory (BPI).[29] BPI items were average pain, worst pain and pain interference with sleep the past 24 hours, all scored at a 0-10 numerical rating scale (NRS). Quality of life was patient reported by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core30 (QLQ-C30, version 3.0).[30] The QLQ-C30 incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea/vomiting); and a global health/quality-of-life (QoL) scale consisting of two items. Six single item scales assess symptoms (dyspnoea, appetite loss, sleep disturbance, constipation and diarrhoea) and the perceived financial impact of having cancer.

Health care personnel reported measures

The following demographic and clinical variables were obtained by health care personnel: age, gender, weight, height, concomitant diseases, previous known history of alcoholism or drug abuse, department category (i.e. inpatient and out-patients clinic), haemoglobin serum concentrations, cancer diagnosis and metastases, and time interval since the cancer disease was diagnosed. All medications and dosages including opioids for the foregoing 24 hours, duration of opioid treatment, and use of rescue opioids in last 24h and route of opioid administration were registered. Oral daily morphine equivalent dose was calculated.[14] Performance status was rated using the Karnofsky performance status (KPS) which ranges from 0 (i.e., dead) to 100 (i.e., normal activity) scale.[31]

Cognitive function was assessed by the Mini Mental State Exam (MMSE). The MMSE consists of 20 items and has a total score of 30 points.[32]

Statistical analysis

Means, standard deviations and range were reported for all scale variables. Sleep characteristics were given as mean values of the seven component scores and for the PSQI global scores from the PSQI. Univariate association between PSQI global scores and pain average and worst pain intensity, quality of life outcomes, oral daily morphine equivalent opioid dose and number of days on opioids were reported by Spearman`s rank correlation coefficients (r_s).

To examine predictive factors of PSQI global scores a multiple regression model was constructed. PSQI global score (0-21) was used as the outcome variable. Bivariate linear regression was used to select symptoms and characteristics as potential predictors in the linear multivariate analyses of PSQI global scores. The significance level to include a variable in the multivariate analyses was $p < 0.10$. Variables that were included in the model were: pain intensity from the BPI and global health QoL, physical function, emotional function, and the symptom scales fatigue, dyspnoea, constipation and financial difficulties from the QLQ-C30. In addition, oral daily morphine equivalent dose, days on opioids and KPS were included in the backward elimination analyses. A p-value < 0.01 was applied for removing variables.

Data were analysed by IBM SPSS Statistics version 20.0 for Windows (IBM Corporation, Armonk, USA).

RESULTS

A total of 931 patients from nine hospitals located in five countries were recruited from February 2004 to April 2008 (Denmark n= 30, Germany n= 452, Lithuania n= 54, Norway n= 331 and Switzerland n= 64). Of the patients, 327 patients did not complete the PSQI (too sick n= 153, did not want to n= 91 and unknown reason n= 83). A total of 604 patients were included in the analyses.

Sample characteristics

Demographics and clinical characteristics are shown in table 1. Of the 604 patients, 42% were female. The median age was 62 years. Mean KPS was 62.5 (±14.2). Twelve percent of the patients had a KPS of 50 or lower, corresponding to an ECOG Performance status III-IV. The mean oral daily morphine equivalent dose was 303 mg/24 h (±543.8 mg). The four main cancer diagnoses in the cohort were gastro- (23.1%), lung- (18.7%), prostate- (15.2%) and breast cancer (10.8%). The majority (84.1%) had one or more metastases. The mean MMSE score was 27.3 (±3.2; 12-30).

Table 1 Demographic and cancer related patient characteristics (n=604)

Characteristics	N (Per-cent)[1,2]
Female, Gender	253 (42)
Karnofsky Performance status score[3], mean (SD; min-max)	62.5 (14.2; 20-100)
Age, years, median, (min-max)	62 (20-91)
Body mass index, mean, (SD; min-max)	23.5 (4.6; 13.8-43.2)
Treatment setting; inpatient/outpatient	460 (76.2)/144 (23.8)
Cancer diagnosis:	
Gastro intestinal/liver/pancreas	140 (23.2)
Lung cancer/mesothelioma	113 (18.7)
Prostate cancer	92 (15.2)
Breast cancer	65 (10.8)
Urological cancer	51 (8.4)
Head and neck cancer	39 (6.5)
Female reproductive organs	25 (4.1)
Haematological cancer	25 (4.1)
Skin cancer	17 (2.8)
Sarcoma	15 (2.5)
Unknown origin	14 (2.3)
Other cancer	8 (1.3)
Time since cancer diagnosis, median days (min-max)	15.00 (0-286)
Metastasis, present	508 (84.1)
Bone	287 (47.5)
Liver	152 (25.2)
Lung	124 (20.5)
CNS	28 (4.6)
Oral daily morphine equivalent dose (mg), mean(SD; min-max)	303 (543.8; 10-8064)
Number of days on opioids, mean (SD; min-max)	186 (345.3; 3-2418)
Previous known abuse of alcohol or drugs	44 (7.3)
Haemoglobin serum concentrations[4] mean (SD; min-max)	11.4 (1.6; 7.3-16.1)
Use of medication that may influence sleep:	
Steroids	239 (39.6)
Antidepressants	130 (21.5)
Benzodiazepines	106 (17.5)
Hypnotics	74 (12.3)
Co-morbidities	
Heart disease	145 (24.0)
Vascular disease	92 (15.2)
Lung disease	60 (9.9)
Neurological disease	25 (4.1)
Psychiatric disease	21 (3.5)

[1] Unless otherwise specified, [2] Missing values were <3% for all variables, expect for "Body mass index" (5.8 % missing), "Number of days on opioids" (7.8 % missing) and "Time since cancer diagnosis" (9.7 % missing), [3]Karnofsky performance status using a 0 (i.e., dead) to 100 (i.e., normal activity) scale,[31] [4] g/dl

Sleep quality and cancer related characteristics

The majority of the patients (78%) were categorized as having poor sleep quality (PSQI global scores >5). The mean PSQI global score was 8.8 (±4.2; range 0-20). The distribution of global PSQI scores is given in fig.1. Descriptive statistics of sleep quality on the seven components scores of the PSQI are shown in table 2. The component from the PSQI that was most affected was "sleep disturbance" with a mean score of 1.6 (±0.7; 0-3). Forty-four percent of the patients reported having trouble sleeping because of pain three or more times a week, 57% reported trouble sleeping because of having to use the bathroom during the night for three or more times a week and 27% had trouble sleeping because of waking up in the middle of the night or early morning for three or

more times a week. One-third of patients reported trouble sleeping because of difficulty initiating sleep for three or more times a week.

(Insert figure 1)

Table 2 Descriptive statistics of sleep quality and cancer related symptoms

	Mean	SD	Min	Max	Missing (%)
Sleep[1]					
PSQI global score	8.8	4.2	0	20	11.0
Subjective sleep quality	1.4	0.8	0	3	2.6
Sleep latency	1.3	1.0	0	3	7.3
Sleep duration	0.7	1.0	0	3	5.1
Habitual sleep efficiency	1.3	1.2	0	3	10.4
Sleep disturbance	1.6	0.7	0	3	8.8
Use of sleep medication	1.3	1.4	0	3	3.5
Daytime dysfunction	1.5	0.1	0	3	5.3
Pain[2]					
Average pain	3.6	2.2	0	10	5.0
Worst pain	5.1	2.7	0	10	2.2
Health related QoL[3]					
Global health QoL[3a]	35.8	21.5	0	91.67	3.3
Physical function[3a]	37.0	24.6	0	100	1.5
Emotional function[3a]	54.6	27.5	0	100	1.5
Fatigue[3b]	70.6	22.9	0	100	1.7
Nausea and vomiting[3b]	29.4	30.7	0	100	1.3
Dyspnoea[3b]	38.1	36.2	0	100	2.2
Diarrhoea[3b]	16.5	28.0	0	100	2.8
Constipation[3b]	49.8	38.4	0	100	1.7
Financial difficulties[3b]	31.5	37.1	0	100	3.5

[1] Sleep quality assessed by the Pittsburgh Sleep Quality Index (PSQI)[28]

[2] Pain intensity assessed by the Brief Pain Inventory, numerical rating scale 0-10[29]

[3] Health related quality of life assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (QLQ-C30). [30]

[3a] QLQ-C30 functioning scale (0-100). A high score on the functional scales/Global QoL scale means a good function/quality of life. [3b]QLQ-C30 symptom scale (0-100). A high score on symptom scales denotes higher symptom burden.

Twenty-five percent of the patients reported that pain severely interfered with sleep (NRS 7-10). Corresponding numbers for pain to moderately interfere (NRS 4-6) or to mildly interfere (NRS 1-3) with sleep were 24% and 26%, respectively. A quarter of the patients reported that pain did not interfere with sleep (NRS 0).

The mean value of average pain assessed by the BPI was 3.6 (±2.2; 0-10). The mean value of the global health QoL scale was 35.8 (±21.5; 0-91.7). The fatigue scale of the QLQ-C30 received the highest mean score 70.6 (±22.9; 0-100) (table 2).

Correlations between sleep quality and cancer related symptoms

The correlations between PSQI global scores and pain intensity, dimensions of quality of life, cognitive status and oral daily morphine equivalent dose are shown in table 3. PSQI global scores were correlated with average pain intensity and worst pain intensity (Spearman`s Rho (r_s)=0.201 and 0.164; P<0.001, respectively). Statistically

significant negative correlations were seen between PSQI global scores and global health QoL (r_s= -0.131; p=0.003), physical function (r_s=-0.149; p=0.001) and emotional function (r_s=-0.344; P<0.001). Statistically significant correlations were observed between PSQI global scores and the symptom scales dyspnoea and constipation (r_s=0.148; p=0.001, r_s=0.212; P<0.001, respectively). Fatigue and financial difficulties from the QLQ-C30 correlated both to PSQI global scores (r_s=0.244 and 0.270; P<0.001, respectively). There was a correlation between PSQI global scores and oral daily morphine equivalent dose (r_s=0.137; P=0.002). KPS was negatively correlated with PSQI global scores (r_s=-0.168; P<0.001).

Table 3 Correlations between sleep quality and pain intensity and other cancer related variables

	PSQI global score[1]	
	Spearman's Rho	P-value
Pain intensity, average pain[2]	0.201	<0.001
Pain intensity, worst pain[2]	0.164	<0.001
Global health QoL [3a]	- 0.131	0.003
Physical function[3a]	- 0.149	0.001
Emotional function[3a]	- 0.344	<0.001
Fatigue[3b]	0.244	<0.001
Nausea and vomiting[3b]	0.079	0.067
Dyspnea[3b]	0.148	0.001
Diarrhea[3b]	0.018	0.680
Constipation[3b]	0.212	<0.001
Financial difficulties[3b]	0.270	<0.001
Cognitive status[4]	0.005	0.911
Oral daily morphine equivalent dose[5]	0.137	0.002
Days on opioids[6]	- 0.029	0.521
Karnofsky performance status[7]	- 0.168	<0.001

[1] Sleep quality assessed by the Pittsburgh Sleep Quality Index (PSQI) global score (0-21)[28]

[2] Pain intensity assessed by the Brief Pain Inventory, numerical rating scale 0-10[29]

[3] Health related quality of life assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (QLQ-C30).[30]

[3a] QLQ-C30 functioning scale (0-100). A high score on functional scales means a good function/quality of life, [3b] QLQ-C30 symptom scale (0-100). A high score on symptom scales means severe symptoms and hence a poor quality of life.

[4] Assessed by the Mini Mental State Exam (MMSE)[32]

[5] Oral daily morphine equivalent dose (mg/24 h)

[6] Number of days on opioid treatment before inclusion day in the present study

[7] Performance status was rated using the Karnofsky performance status using a 0 (i.e., dead) to 100 (i.e., normal activity) scale[31]

Predictors for sleep quality

The bivariate analyses identified pain intensity, global health QoL, physical and emotional function, fatigue, dyspnoea, constipation, financial difficulties, oral daily morphine equivalent dose and KPS as potential predictors in the multivariate analyses of PSQI global scores (0-21) (Table 4). The significant predictors of PSQI global scores in the multiple regression model were pain intensity, emotional function, constipation, financial difficulties and KPS. The regression model explained 21% of the total variance (Table 4).

Table 4 Bivariate and multiple linear regression models of associating factors and predictors of sleep quality (PSQI global score[1]). Unstandardized regression coefficients (B), Standard Error (SE) and 95 % Confidence Intervals (95% CI)

	Bivariate linear regression model				Multiple linear regression model, backward method			
Independent variables	B	SE	95& CI	P	B	SE	95& CI	P
Constant					10.273	0.959	8.389 to 12.158	<0.001
Pain intensity[2]	0.391	0.082	0.230 to 0.552	<0.001	0.191	0.079	0.035 to 0.347	0.016
Global health QoLe[3a]	-0.025	0.008	-0.042 to -0.008	0.003				
Physical function3[a]	-0.027	0 007	-0.041 to -0.012	<0.001				
Emotional function3[a]	-0.052	0.006	-0.064 to -0.040	<0.001	-0.037	0.007	-0.050 to -0.023	<0.001
Fatigue[3b]	0.043	0.008	0.028 to 0.058	<0.001				
Nausea and vomiting[3b]	0.008	0.006	-0.004 to 0.020	0.186				
Dyspnea[3b]	0.017	0.005	0.007 to 0.027	0.001				
Diarrhea[3b]	0.004	0.007	-0.009 to 0.017	0.562				
Constipation[3b]	0.023	0.005	0.014 to 0.032	<0.001	0.017	0.004	0.009 to 0.026	<0.001
Financial difficulties[3b]	0.031	0.005	0.022 to 0.040	<0.001	0.020	0.005	0.010 to 0.030	<0.001
Cognitive function[4]	-0.038	0.060	-0.155 to 0.079	0.525				
Oral daily morphine equivalent dose[5]	0.001	0.000	0.000 to 0.002	0.013				
Days on opioid[6]	0.000	0.001	-0.001 to 0.001	0.419				
Karnofsky performance status[7]	-0.049	0.013	-0.074 to -0.025	<0.001	-0.026	0.012	-0.050 to -0.002	0.034
Adjusted R Square					0.211			

[1] Sleep quality assessed by the Pittsburgh Sleep Quality Index (PSQI) global score (0-21)[28]

[2] Pain intensity assessed by the Brief Pain Inventory by pain on the average on a numerical rating scale 0-10[29]

[3] Health related QoL assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (QLQ-C30)[30]

[3a] QLQ-C30 functioning scale (0-100) a high score on functional scales means a good function/quality of life

[3b] QLQ-C30 symptom scale (0-100). A high score on symptom scales means severe symptoms and hence a poor quality of life.

[4] Assessed by the Mini Mental State Exam (MMSE)[32]

[5] Oral daily morphine equivalent dose (mg/24 h)

[6] Number of days on opioid treatment before inclusion day in the present study

[7] Karnofsky performance status using a 0 (i.e., dead) to 100 (i.e., normal activity) scale[31]

DISCUSSION

Interpretation of main findings

In this large, international multi-centre study, we found that the majority (78%) of the 604 patients with advanced cancer treated with a WHO step III opioid for cancer pain had poor sleep quality as measured by the PSQI. PSQI global scores were statistically significantly correlated with worse outcomes in pain intensity, physical function, emotional function, fatigue, dyspnoea, constipation, financial difficulties, KPS and higher oral daily morphine equivalent doses. However, the magnitude of the correlations was moderate (range from -0.35 to 0.15). Pain intensity, emotional function, constipation, financial difficulties and KPS were found to be significant predictors of poor sleep quality in the multiple regression model.

Previous studies have generally demonstrated prevalence of sleep disturbances ranging from 23 to 96 percent in patients with advanced cancer disease.[6, 8, 12, 23-25, 33] These results are obtained from various cancer populations such as out-patients,[33] patients with a specific cancer diagnosis,[25] and unselected palliative care patients.[8] The studies have also used various instruments to report sleep disturbances such as Athens Insomnia Scale,[8] the Insomnia Severity Index,[24] and PSQI.[9, 33] The significance of the choice between instruments is demonstrated by Yennurajalingam et al. who observed in a cohort of cancer patients that a NRS sleep score did not reflect the variability in PSQI scores.[12]

Sleep disturbance can be related to both pain and the use of opioids.[11-13, 17] In the present study, most patients reported that pain interfered with sleep and pain intensity was a statistically predictor of poor sleep quality measured by the PSQI. The relation between poor PSQI sleep quality and pain agree with results from previous studies.[9, 12, 19, 24] Opioids may improve sleep by their pain relieving and sedative effects. However, opioids may also interact with central nervous mechanisms influencing sleep rhythms negatively.[18, 34] Also the relationship between the use of opioids and sleep may change due to development of tolerance of opioids effects.[17] Previous studies have either not reported the use of opioids or assessed the use of opioids as a binary yes/no variable. In this study, including a selected cohort with all using a WHO step III opioid, we observed a high prevalence of sleep disturbance. The daily dose and duration of opioid therapy were not a statistically significant contributor to the explained variation in sleep quality on the PSQI score.

Emotional function, financial difficulties and constipation were significant predictors of sleep quality in the multiple regression model in this study. Emotional function in the QLQ-C30 encompasses four items: feeling tense, being worried, being irritable and feeling depressed. Patients with lower scores on emotional function reported more sleep disturbance. This result is consistent with previous research where sleep disturbance is associated with increased frequency of depression and a worse sense of well-being.[6, 12] Secondly, financial difficulties were a significant predictor of poor sleep in the multiple regression model in this study. Self-reported "financial burden" or "financial stress" is common among cancer patients,[35] but calls for further investigation as there may be some overlap or interaction between emotional function/worries and financial difficulties as assessed by the QLQ-C30.

Thirdly, constipation was one of the symptom scales from the QLQ-C30 questionnaire that was observed as a predictor of poor sleep quality in the present study. Opioids are associated with significant gastrointestinal adverse

effects that impair patients quality of life,[36] and constipation is common in palliative care patients.[37] Gastrointestinal discomfort may well disturb sleep quality. However, because of the cross-sectional design of the present study, we cannot determine if constipation caused poor sleep quality or if constipation and poor sleep is co-existing symptoms.

In addition to cancer related symptoms, the multivariate regression analyses showed that the patient's performance status was a significant predictor of PSQI global score. Karnofsky performance status reflects the patient`s ability to carry on normal activities, or the patient`s degree on dependence on help and nursing care.[31] Poor functional performance was associated with poor sleep. This result is consistent with a Italian study in patients with advanced cancer where sleep, measured by the Athens insomnia scale, was significantly associated with lower KPS levels.[38]

Sleep quality consists of several aspects, such as sleep duration and latency or number of arousals.[28] This is reflected by the PSQI, which measures seven different aspects of sleep quality. We found that in this cohort of patients with advanced cancer who were treated with a WHO step III opioid, all seven components of sleep quality were affected (Table 2). This means that sleep disturbance in cancer pain patients is a complex mix of difficulty initiating sleep, difficulties to stay asleep, early wakening and various external factors disturbing sleep such as having to use the bathroom, cannot breathe comfortably, feeling to cold or hot, or having pain.

Strengths and Limitations

Strengths of this study are the relatively large number of patients that were recruited from hospitals in several countries, and the use of an instrument developed specifically for assessment of sleep quality. Moreover, it includes palliative care patients only, for whom findings are clinically relevant. Limitations include the cross-sectional design. In this cohort of patients with advanced cancer, the nature of the relationship between pain and sleep quality is considered to be quite complex and it might be that the relationship is reciprocal.[39] Because of the cross-sectional design, we cannot draw any conclusion regarding the direction of the relationship between pain and sleep quality. Another limitation is that factors included in the multivariate regression model explained only 21% of the variability of the sleep quality. Thus, other hereto-unknown factors are important for sleep quality. It would have been of interest to examine the difference in sleep quality in patients with and without opioid treatment. However, groups of cancer patients using no opioids versus those in need of opioid therapy will usually be at different stages of their cancer disease and difficult to compare. Finally, the data reported in this study were obtained almost a decade ago and changes in palliative care may have altered the prevalence of sleep disturbances. On the other hand, recent data show that the prevalence of sleep disturbances in cancer is still high,[8, 9, 12] thereby arguing it is still important to address this symptom.

Clinical implications

Knowledge of symptom prevalence is important for clinical practice.[5] The high prevalence of sleep disturbance and the impact on sleep quality of cancer related variables such as pain intensity, emotional function, constipation, financial difficulties and KPS, highlights the clinical relevance of this problem in patients with advanced cancer using a WHO step III opioid for cancer pain. All dimensions of sleep quality were affected, suggesting that sleep disturbances in cancer pain patients represents several clinical challenges. As with other symptoms, it is important to categorize and classify sleep disturbances in order to address each patient's individual needs. In this study, sleep

quality measured by PSQI is statistically related to other medical problems that could be assessed and treated per se and maybe have beneficial effect on sleep: pain intensity, emotional function, fatigue and constipation.

Only 12% of the patients in this cohort used hypnotics. Nevertheless, most patients (78%) reported poor sleep quality. This might illustrate that sleep disturbance is undertreated or that the use of hypnotics is not the best treatment of sleep disturbance in this cohort. Moreover, patients with advanced cancer rarely present with a single symptom. Hence, there is a need for a comprehensive assessment of symptom burden in which sleep quality is one of many.

Conclusions

In this multinational, multicenter study we included a large number of cancer patients using a WHO step III opioid and applied a designated sleep questionnaire; the PSQI. We observed that the majority of the patients reported poor total sleep quality. Sleep was influenced for all sleep components. This calls for special attention to sleep quality in patients with advanced cancer. In order to identify and treat patients with sleep disturbances health care personnel should routinely assess sleep problems using patient reported outcome measures. More research is needed to examine the effects of opioids on sleep quality.

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STATEMENTS

Contributors GJ, SK and PK were responsible for the conception of the study. GJ, SK, MK, RS and PK collected the data which were analysed by GJ, PF and PK. Data were interpreted by GJ, ME, PF, MJH and PK and confirmed by all authors. All authors were involved in drafting and critically appraising the manuscript before providing final approval

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Ethics approval Regional Medical Research Ethics Committee (ref 119-03), and the study was approved by ethical committees at each study centre or in each country before initialization

Licence for Publication

Competing Interest: None declared

Figure legend: Figure 1 Frequency distribution of global PSQI scores. Mean = 8.83, standard deviation = 4.18. PSQI global scores >5 indicates poor sleep

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