

Observational study of sleep disturbances in advanced cancer

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ABSTRACT

Objectives To determine the prevalence of nightmares, sleep terrors and vivid dreams in patients with advanced cancer (and the factors associated with them in this group of patients).

Methods The study was a multicentre, prospective observational study. Participants were patients with locally advanced/metastatic cancer, who were under the care of a specialist palliative care team. Data were collected on demographics, cancer diagnosis, cancer treatment, current medication, performance status, sleep quality (Pittsburgh Sleep Quality Index), dreams and nightmares, and physical and psychological symptoms (Memorial Symptom Assessment Scale-Short Form).

Results 174 patients completed the study. Sleep quality was poor in 70.5% participants and was worse in younger patients and in inpatients (hospital, hospice). 18% of patients reported nightmares, 8% sleep terrors and 34% vivid dreams. Nightmares were associated with poor sleep quality and greater sleep disturbance; nightmares were also associated with greater physical and psychological burden. Nightmares (and vivid dreams) were not associated with the use of opioid analgesics.

Conclusions Nightmares do not seem to be especially common in patients with advanced cancer, and when they do occur, there is often an association with sleep disturbance, and/or physical and psychological burden.

INTRODUCTION

To die, to sleep - to sleep, perchance to dream - ay, there's the rub, for in this sleep of death what dreams may come...

(from *The Tragedy of Hamlet, Prince of Denmark* by William Shakespeare)

Certain sleep disorders are common in patients with cancer and more common than in the general population (ie, insomnia, circadian rhythm sleep wake disorders).^{1 2} These sleep disorders can occur at any stage of the disease, but

are especially common in patients with advanced disease.^{3 4} However, the medical literature contains very little data on other sleep problems in patients with cancer, including nightmares, sleep/night terrors and so-called 'vivid dreams'.

The International Classification of Sleep Disorders, Third Edition (ICSD-3) describes nightmares as 'frightening dreams awakening the patient from sleep'.¹ Nightmares are relatively common,⁵ but the related sleep disorder (nightmare disorder) is much less common¹; the diagnostic criteria for nightmare disorder include 'repeated occurrences', and 'the dream experience, or sleep disturbance produced by awakening from it, causes clinically significant distress or impairment in social, occupational, or other areas of functioning'.¹ The ICSD-3 describes sleep terrors (also known as night terrors) as arousals from non-rapid eye movement (REM) sleep, which are 'characterized by episodes of abrupt terror, typically beginning with an alarming vocalization such as a frightening scream'.¹ One of the features of a sleep terror (vs a nightmare) is that the patient is usually confused/disorientated on awakening.¹ The ICSD-3 does not define the term 'vivid dreams', but the following description has been in a previous study: 'unusually clear, long dreams with elaborate scenario and possibly strong emotions, that occurred only when sleeping and were acutely remembered'.⁶

The aim of the current study was to investigate sleep disturbance and specifically nightmares, sleep terrors and vivid dreams in a heterogeneous group of patients with advanced cancer. The objectives of the study were to determine the prevalence of these phenomena, and the factors associated with them (ie, demographics, cancer status, performance status, sleep quality, physical symptoms, psychological symptoms, use of opioid analgesics), in this group of patients.



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METHODS

The current study was a prospective observational study involving inpatients and outpatients receiving specialist palliative care at one hospital (Royal Surrey County Hospital, Guildford) and three hospices (St. Catherine's Hospice, Crawley; Sam Beare Hospice, Weybridge; Woking Hospice, Woking) in the UK. The study was sponsored by the Royal Surrey County Hospital, and ethical committee approval was obtained from the National Research Ethics Service (NRES) Committee London—Bloomsbury.

The study was open to all patients who fulfilled the inclusion/exclusion criteria. The inclusion criteria for the study were (1) age ≥ 18 years, (2) locally advanced/metastatic cancer, (3) completed primary cancer treatment and (4) referred to specialist palliative care team. The exclusion criteria for the study were (1) unable to give written (informed) consent and (2) unable to complete questionnaire. Consecutive recruitment was undertaken at all study sites.

Written consent was obtained prior to entry into the study; participants were given an information sheet about the study, and also the opportunity to ask questions of the researchers (and the opportunity to discuss participation with other people), as part of the consent process. The study consisted of a single interview, with additional information being obtained from the clinical records (as required). Data were collected on demographics, cancer diagnosis, cancer treatment (current), comorbidities and medication (current). Participants were asked to assess their own performance status (using the Eastern Cooperative Oncology Group (ECOG) scale)⁷ and to complete the Memorial Symptom Assessment Scale—Short Form (MSAS-SF)⁸ and the Pittsburgh Sleep Quality Index (PSQI).⁹

The MSAS-SF is a patient-completed, validated questionnaire that assesses 26 physical and 6 psychological symptoms; it asks about the presence of the symptom and (if present) 'how much did it distress or bother you'? The PSQI is a patient-completed, validated questionnaire that assesses sleep quantity and sleep quality; it consists of 19 questions in total, with 14 questions being used for 'scoring' purposes. Thus, the PSQI generates a series of so-called 'component' scores (ie, duration of sleep, sleep disturbance, sleep latency, day dysfunction due to sleepiness, sleep efficiency, overall sleep quality, needs medications to sleep) and a total score that categorises patients as having 'poor sleep quality' or 'good sleep quality'.¹⁰ The PSQI has been validated in patients with cancer¹¹ and used in previous studies involving patients with advanced cancer.³

Participants were also asked about the presence of nightmares, sleep terrors and vivid dreams in the last month (using definitions derived from the ICSD-2 and the Cohen *et al* study^{6,12}); if present, they were asked to state the frequency (ie, less than once a week, once or twice a week, three or more times a week). In the case of nightmares, they were also asked about the

distress caused by the nightmares (not at all, a little bit, somewhat, quite a bit, very much), the content of the nightmares, any communications about the nightmares and any interventions for the nightmares.

The sample size for the study ($n=174$) was calculated from the reported prevalence of nightmares in the general (Norwegian) population.⁵ In terms of the statistical analysis, a case of nightmares (and sleep terrors/vivid dreams) was defined as a participant experiencing at least one nightmare during the previous month. The proportion of participants experiencing nightmares (and sleep terrors/vivid dreams) was calculated and the 95% CIs determined using adjusted Wald's methods.

The association between nightmares (and sleep terrors/vivid dreams) and relevant variables were analysed using χ^2 or Fishers' exact test for categorical variables, and t-test or Mann-Whitney U test for continuous variables. The variables investigated were demographics, cancer diagnosis, cancer treatment, performance status, treatment setting, opioid medication, physical symptoms, psychological symptoms and sleep quality. Multivariate analysis was not undertaken (as planned) due to the small number of participants experiencing nightmares.

RESULTS

One hundred and seventy-four individuals participated in the study, and table 1 shows the characteristics of the participants. Eighty-two per cent of participants were receiving opioid analgesics. The median number of symptoms identified by the MSAS-SF was 13 (range 2–31), with a median number of seven physical symptoms (range 1–11) and a median number of three psychological symptoms (range 1–6).

Table 2 shows the data from the PSQI. Participants reported a median time to 'fall asleep' of 15 min (range 1–240 min) and a median time of 'actual sleep' of 6.5 hours (range 1.5–12.0 hours). The PSQI sleep quality was good in 29.5% participants (ie, total score ≤ 5) and poor in 70.5% participants (ie, total score > 5). Poor PSQI sleep quality was associated with younger age ($r=-0.2539$; $p=0.001$) and inpatient setting ($p=0.041$), but was not associated with gender, cancer diagnosis, cancer treatment, ECOG performance status or use of opioids. Table 3 shows the data for the PSQI components.

Nightmares

The prevalence of nightmares within the previous month was 18% (95% CI 12.8 to 24.2), with 21 (68%) participants reporting nightmares less than once a week, 4 (13%) once or twice per week and 6 (19%) three to four times per week. Nightmares were associated with age; the median age of participants with nightmares was 64 years, while the median age of participants without nightmares was 67 years ($p=0.005$). However, there was no association with gender, cancer diagnosis,

Table 1 Study participants

Characteristic	Frequency (n=174)
Age	Median—66 years Range—35–90 years
Gender	Female—100 (57.5%) Male—74 (42.5%)
Cancer diagnosis	Gastrointestinal—62 (35.5%) Urological—24 (14%) Breast—28 (16%) Lung—21 (12%) Gynaecological—13 (7.5%) Head and neck—8 (4.5%) Haematological—5 (3%) Skin—5 (3%) Neurological—2 (1%) Unknown—6 (3.5%)
Cancer treatment (current)	None—100 (58%) Chemotherapy—49 (28%) Radiotherapy—9 (5%) Other (eg, hormone, biological)—16 (9%)
ECOG performance status	0–6 (3.5%) 1–40 (23%) 2–42 (24%) 3–72 (41.5%) 4–14 (8%)
Setting	Hospital—115 (66%) Hospice—59 (34%) Inpatient—128 (73.5%) Outpatient—46 (26.5%)

ECOG, Eastern Cooperative Oncology Group.

cancer treatment, ECOG performance status, setting or use of opioids ($p=0.295$). Nightmares were associated with a higher number of symptoms on MSAS-SF (median of 20 symptoms vs 12 symptoms; $p<0.001$), a higher physical subscale score ($p=0.023$), a higher psychological subscale score ($p=0.010$) and a higher global distress index score ($p=0.006$).

In terms of the PSQI components, nightmares were associated with poor sleep quality from the PSQI ($p=0.044$), and the related sleep disturbance component ($p=0.007$), sleep latency component ($p=0.039$), day dysfunction due to sleepiness component ($p<0.001$) and the needs medications to sleep component ($p=0.043$).

Among the 10 (6%) participants with regular (at least once a week) nightmares, the distress caused was ‘a little bit’ in two cases, ‘somewhat’ in one case, ‘quite a bit’ in five cases and ‘very much’ in two cases. However, only five (50%) participants had reported the nightmares to their doctor/nurse (or family), only one participant had received treatment for the nightmares (ie, night sedation) and only two other participants wanted treatment for the nightmares. Six (60%) participants experienced recurring themes within the nightmares, although they often experienced more than one theme (eg, their current illness, five people; death and dying, five people; events in their past, four people; other themes, two people).

Table 2 Pittsburgh Sleep Quality Index (PSQI) question data

PSQI question (and options)	Frequency (n=174)
During the past month, how often have you had trouble sleeping because you cannot get to sleep within 30 min?	
Not during the past month	75
Less than once a week	17
Once or twice a week	30
Three or more times a week	52
During the past month, how often have you had trouble sleeping because you wake in the middle of the night or early morning?	
Not during the past month	32
Less than once a week	13
Once or twice a week	23
Three or more times a week	105
No response	1
During the past month, how often have you had trouble sleeping because you have to get up to use the bathroom?	
Not during the past month	40
Less than once a week	13
Once or twice a week	20
Three or more times a week	101
During the past month, how often have you had trouble sleeping because you cannot breathe comfortably?	
Not during the past month	132
Less than once a week	11
Once or twice a week	13
Three or more times a week	18
During the past month, how often have you had trouble sleeping because you cough or snore loudly?	
Not during the past month	135
Less than once a week	10
Once or twice a week	11
Three or more times a week	17
No response	1
During the past month, how often have you had trouble sleeping because you feel too cold?	
Not during the past month	148
Less than once a week	12
Once or twice a week	10
Three or more times a week	3
No response	1
During the past month, how often have you had trouble sleeping because you feel too hot?	
Not during the past month	94
Less than once a week	24
Once or twice a week	28
Three or more times a week	27
No response	1
Question (and options)	Frequency (n=174)
During the past month, how often have you had trouble sleeping because you had bad dreams?	
Not during the past month	134
Less than once a week	14
Once or twice a week	17
Three or more times a week	9
During the past month, how often have you had trouble sleeping because you have pain?	

Continued

Research

Table 2 Continued

Question (and options)	Frequency (n=174)
Not during the past month	65
Less than once a week	18
Once or twice a week	25
Three or more times a week	66
During the past month, how often have you had trouble sleeping because you have 'other reasons'?	
Not during the past month	128
Less than once a week	8
Once or twice a week	8
Three or more times a week	30
During the past month, how would you rate your sleep quality overall?	
Very good	27
Fairly good	70
Fairly bad	48
Very bad	29
During the past month, how often have you taken medicine to help you sleep (prescribed or 'over the counter')?	
Not during the past month	129
Less than once a week	10
Once or twice a week	9
Three or more times a week	26
During the past month, how often have you had trouble staying awake while driving, eating meals or engaging in social activity?	
Not during the past month	107
Less than once a week	8
Once or twice a week	24
Three or more times a week	34
No response	1
During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?	
No problem at all	31
Only a very slight problem	44
Somewhat of a problem	60
A very big problem	38
No response	1

Sleep terrors

Fourteen participants reported sleep terrors within the previous month (prevalence, 8%; 95% CI 4.8 to 13.2), with nine (64%) reporting this phenomena less than once a week, two (14%) once or twice a week, and three (22%) three or more times a week. Sleep terrors were not associated with age, gender, cancer diagnosis, cancer treatment, ECOG performance status, setting or use of opioids ($p=1.000$). Sleep terrors were associated with a greater number of total symptoms on the MSAS-SF (median of 20 symptoms vs 12 symptoms; $p=0.004$). However, there was no statistically significant association with the physical subscale score, the psychological subscale score or the global distress index.

Night terrors were not associated with poor sleep quality on PSQI ($p=0.348$), but were associated with the related sleep disturbance component ($p=0.048$)

Table 3 Pittsburgh Sleep Quality Index (PSQI) component data

PSQI component (and scores*)	Frequency (n=174)
Duration of sleep	
0	82
1	22
2	25
3	40
Missing data	5
Sleep disturbance	
0	4
1	70
2	85
3	13
Missing data	2
Sleep latency	
0	57
1	43
2	40
3	29
Missing data	5
Day dysfunction due to sleepiness	
0	24
1	76
2	39
3	33
Missing data	2
Sleep efficiency	
0	60
1	23
2	23
3	68
Missing data	0
Overall sleep quality	
0	27
1	70
2	48
3	29
Missing data	0
Needs medications to sleep	
0	129
1	10
2	9
3	26
Missing data	0

*0=minimum score/better; 3=maximum score/worse.

and day dysfunction due to sleepiness component ($p=0.032$).

Vivid dreams

Sixty participants reported vivid dreams within the previous month (prevalence, 34.5%; 95% CI 27.8 to 41.8), with 25 (42%) reporting this phenomena less than once a week, 13 (21.5%) once or twice a

week and 22 (36.5%) three or more times a week. Vivid dreams were not associated with gender, cancer diagnosis, cancer treatment, ECOG performance status, setting or use of opioids ($p=1.000$). However, they were associated with age: the median age of participants with vivid dreams was 63 years, while the median age of participants without vivid dreams was 67 years ($p=0.013$). Vivid dreams were associated with a greater number of total symptoms on the MSAS-SF (median of 16 symptoms vs 12 symptoms; $p=0.001$) and a higher psychological subscale score ($p=0.028$).

Vivid dreams were associated with poor sleep quality on PSQI ($p=0.001$) and the related sleep disturbance component ($p<0.001$), sleep latency component ($p=0.016$), day dysfunction due to sleepiness component ($p=0.004$) and the needs medications to sleep component ($p=0.008$).

DISCUSSION

The results of this study confirm that sleep quality is often poor in patients with advanced cancer.^{3,4} Moreover, the study found an association between inpatient setting and poor sleep quality, which is well reported in the literature (and completely understandable).¹³

Dreaming is a normal activity, which occurs primarily during REM sleep: ~80% of awakenings during REM sleep, and a 'small percentage' of awakenings during non-REM sleep, result in dream recollection.¹⁴ REM sleep accounts for ~20% sleep in young adults, and the REM/non-REM sleep cycle lasts for ~90 min. Unsurprisingly, increased awakenings are associated with increased dream recollection.¹⁵

The lifetime prevalence of nightmares in the general (Norwegian) population has been reported as 66.2% (95% CI 63.3% to 69.2%), while the current (last 3 months) prevalence of nightmares was reported as 19.4% (95% CI 17.0% to 21.9%).⁵ Thus, the prevalence of nightmares in the study population appears to be not dissimilar to that in the general population (although the time spans are somewhat different, ie, 1 month vs 3 months). Moreover, <6% our participants reported weekly or more frequent nightmares. Of note, Davidson *et al* reported a prevalence of 18.3% of 'frightening or unpleasant dreams' in the previous 4 weeks among a mixed group of patients with cancer from Canada,¹⁶ while Gibbins *et al* reported a current prevalence of 23% in a group of patients with advanced cancer from the UK.⁴

It has been suggested that nightmares (and vivid dreams) may be an indication of approaching death (ie, last days/weeks).¹⁷ However, we found no association between nightmares and ECOG performance status (which is an established prognostic indicator),¹⁸ and an analysis of end-of-life dreams suggests that 'distressing' dreams are relatively uncommon.¹⁹

Nightmares are reported more frequently in patients with insomnia as compared with the general population.¹⁵ Hence, it is unsurprising that we identified an

association between nightmares and increased sleep disturbance, and overall poor sleep quality. Altered sleep architecture has been reported in people with frequent nightmares, and it has been suggested that sleep disturbance could lead to nightmares (rather than the standard opinion that nightmares lead to sleep disturbance).²⁰ Of note, Davidson *et al* reported a similar association in their study of patients with advanced cancer.¹⁶

Equally, it is unsurprising that we identified an association between nightmares and presence of uncontrolled physical symptoms, and presence of psychological symptoms. Thus, physical/psychological issues are associated with increased sleep disturbance (and so increased sleep awakenings).^{21,22} Other researchers have also reported an association between nightmares and psychological problems in the general population⁵ and in patients with advanced cancer.²³

It is widely believed that opioids are associated with nightmares, and there are some reports in the literature supporting this position in patients with advanced cancer (ie, case reports/caseseries of patients with nightmares who responded to either switching of the opioid or switching of the route of administration of the opioid).^{24,25} However, a review of the literature of opioid-related central nervous system adverse effects concluded that 'there is little evidence to suggest that opioid-induced dreams, nightmares or hallucinations occur in palliative care patients, other than as part of a delirium, perhaps as prodromal symptoms'.²⁶ Moreover, reviews of the literature of drug-induced nightmares only identified case reports suggesting an association between opioids and nightmares (ie, buprenorphine, tramadol).²⁷ In the case of tramadol, induction of nightmares may be related to its noradrenergic/serotonergic effects rather than its opioid effects.²⁸ Our study found no association between opioid analgesia and nightmares, and this finding is supported by a previous study of sleep disorders in patients with advanced cancer.²³

The lifetime prevalence of sleep terrors in the general population has been reported as 10.4% (95% CI 8.5% to 12.3%),⁵ while the current (last 3 months) prevalence of night terrors was reported as 2.7% (95% CI 1.7% to 3.8%). Thus, the prevalence of sleep terrors in the study population appears to be somewhat higher than that in the general population. A review of the literature did not identify any analogous data, and so further research is needed to corroborate/refute this finding. It appears that there are no data on the prevalence of vivid dreams in the general population, but the prevalence in our study (34.5%) was somewhat less than the prevalence in the Gibbins *et al* study (53%).⁴

In conclusion, nightmares do not seem to be especially common in patients with advanced cancer (as compared with the general population), and when they do occur, there is often an association with sleep disturbance, and/or physical and psychological

problems. Patients presenting with nightmares should be assessed for underlying problems, and management should focus on treatment of any underlying problem (rather than specific treatment for nightmares).

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Contributors AND conceived the study. AND and SDP wrote the protocol. SDP, AG and BL were responsible for data collection. AND and SDP wrote the first draft of the manuscript. AG and BL reviewed the manuscript.

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