

# Sleep problems in advanced disease

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## ABSTRACT

**Sleep problems are relatively common in patients with advanced disease, and are associated with significant morbidity in these groups of patients. The focus of this article is sleep problems in patients with advanced cancer, and specifically insomnia, 'vivid' dreams and nightmares. However, other sleep problems are also relatively common in this group of patients, including sleep-related breathing disorders and circadian rhythm sleep-wake disorders. Healthcare professionals should screen all patients with advanced diseases for sleep problems and, equally, initiate appropriate (evidence-based) interventions when they are discovered.**

## Introduction

Sleep is a complex phenomenon, which serves various functions, and which is essential for existence.<sup>1</sup> Sleep problems are common in patients with advanced cancer and in patients with other life limiting conditions.<sup>2</sup> This article focuses on the literature in patients with advanced cancer, but much of the content equally applies to patients with other life limiting conditions.<sup>2</sup>

Sleep is a cyclical process (~90 min per cycle), which consists of two types of sleep (rapid eye movement (REM) sleep and non-REM sleep) and five stages of sleep (stages 1–4 = non-REM sleep, stage 5 = REM sleep).<sup>1,2</sup> The different types/stages of sleep are characterised by distinctive electroencephalogram (EEG) features, and distinctive physical features. For example, REM/stage 5 sleep is characterised by marked EEG activity, muscle hypotonia (on electromyography), fast horizontal eye movements (on electro-oculography) and variability in vital signs.

The American Academy of Sleep Medicine / International Classification of Sleep Disorders categorise sleep disorders into six clinical divisions: insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias and sleep-related movement disorders.<sup>3</sup>

This article focusses on the common symptoms reported by patients with advanced cancer. However, other sleep problems also appear to be common in this group of patients.<sup>2</sup> For example, opioid analgesics (which are often prescribed in patients with advanced cancer) are associated with sleep-related breathing disorders, including central sleep apnoea, obstructive sleep apnoea and ataxic or irregular breathing patterns.<sup>4</sup> Moreover,

these sleep-related breathing disorders are linked not only to increased morbidity (eg daytime sleepiness, cognitive impairment) but also to increased mortality.

## Insomnia

Insomnia has been defined as 'a persistent difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep, and results in some form of daytime impairment'.<sup>3</sup> Patients with advanced cancer often report 'insomnia', and many meet the diagnostic criteria for short-term insomnia disorder (Box 1), or even chronic insomnia disorder (ie the sleep disturbance and associated daytime symptoms have been present for at least 3 months, and the sleep disturbance and associated daytime symptoms occur at least three times per week).<sup>3</sup> However, the prevalence of these sleep disorders is unknown in this group of patients. Nevertheless, researchers have reported that 62–70% patients with advanced cancer had poor sleep quality as assessed by the Pittsburgh Sleep Quality Index.<sup>5,6</sup>

Davies *et al* reported that in their study of 174 patients with advanced cancer, 30% patients had trouble sleeping because they couldn't get to sleep within 30 minutes three or more times a week during the previous month, and that 60% patients had trouble sleeping because they woke in the middle of the night or early morning three or more times a week in the previous month.<sup>5</sup>

## Key points

Sleep problems are common in patients with advanced disease.

Sleep problems are associated with significant morbidity in patients with advanced diseases.

Insomnia is often secondary to related physical symptoms (and psychological problems).

Management of insomnia primarily involves treatment of perpetuating factors, sleep hygiene measures, and non-pharmacological interventions (cognitive behavioural therapy).

KEYWORDS: Palliative care, insomnia, vivid dreams, nightmares, sleep disturbance ■

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### Box 1. Diagnostic criteria for short-term insomnia disorder.

**The patient reports, or the patient's caregiver observes, one or more of the following:**

- > difficulty initiating sleep
- > difficulty maintaining sleep
- > waking up earlier than desired
- > resistance to going to bed on appropriate schedule
- > difficulty sleeping without caregiver intervention.

**The patient reports, or the patient's caregiver observes, one or more of the following related to the night time sleep difficulty:**

- > fatigue/malaise
- > attention, concentration or memory impairment
- > impaired social, family, occupational or academic performance
- > mood disturbance / irritability
- > daytime sleepiness
- > behavioural problems (eg hyperactivity, impulsivity, aggression)
- > reduced motivation/energy/initiative
- > proneness to errors/accidents
- > concerns about or dissatisfaction with sleep.

**The reported sleep/wake complaints cannot be explained purely by inadequate opportunity (ie enough time is allotted for sleep) or inadequate circumstances (ie the environment is safe, dark, quiet and comfortable) for sleep.**

**The sleep disturbance and associated daytime symptoms have been present for <3 months.**

**The sleep/wake difficulty is not explained by another sleep disorder.**

**All above criteria must be met to qualify as short-term insomnia disorder.**

Adapted from Zucconi M, Ferri R. Classification of sleep disorders. In: Bassetti CL, Dogan Z, Peigneux P (eds). *Sleep Medicine Textbook*. Regensburg: European Sleep Research Society, 2014.

It should be noted that the quality of sleep is not always related to the duration of sleep,<sup>7</sup> and that it is often worse among inpatients (as compared to outpatients),<sup>5,8</sup> and often poor among carers (cf general population).<sup>7,9</sup> Indeed, the prevalence of insomnia in carers is not dissimilar to that in patients with advanced cancer.<sup>9</sup>

In most cases, the insomnia develops following the diagnosis,<sup>10,11</sup> and it may be precipitated by the cancer *per se*, the cancer treatment and/or concomitant physical symptoms and psychological problems.<sup>11</sup> Furthermore, it may be perpetuated by similar factors, as well as by environmental factors, maladaptive thinking (relating to sleep) and maladaptive behaviours (relating to 'sleep hygiene').<sup>11</sup> Hugel *et al* reported that in their study of 73 patients with advanced cancer, 60% patients related their insomnia to uncontrolled physical symptoms (predominantly pain and urinary frequency).<sup>10</sup>

Insomnia may be associated with daytime sleepiness, cognitive impairment, accidents/injuries, anxiety,<sup>12</sup> depression,<sup>12</sup> delirium,<sup>13</sup> fatigue and, unsurprisingly, impaired quality of life.<sup>14</sup> Insomnia is associated with suppression of

the immune system, which may have implications in terms of development of infections, and also progression of cancers. Indeed, insomnia has been shown to be associated with a decreased response to chemotherapy, and with a decreased (overall) survival, in an observational study of 361 patients with metastatic colorectal cancer.<sup>15</sup>

The management of insomnia includes treatment of perpetuating factors (eg physical symptoms, psychological problems), sleep hygiene measures (Box 2), non-pharmacological interventions (eg cognitive behavioural therapy, exercise), pharmacological interventions and combination of modalities.<sup>16</sup> Pharmacological interventions should be used with care, restricted to patients with related distress and prescribed for only short periods (and intermittently rather than continuously; Box 3).<sup>17</sup> The choice of hypnotic depends on a variety of factors, including the clinical features of the insomnia.<sup>17</sup>

### Vivid dreams

Vivid dreams (defined as 'unusually clear, long dreams with elaborate scenarios and possibly strong emotions, that occurred only when sleeping and were acutely remembered') appear to

### Box 2. Sleep hygiene measures.

#### Ensure sleep expectations are realistic

Normal sleep duration is 6–10 hours per night; normal sleep pattern includes 1–2 awakenings per night.

#### Wake up at the same time each day (irrespective of sleep duration)

#### Ensure exposure to natural/artificial light after awakening

#### Establish a 'clear your head time' in early evening

Set aside 30–45 minutes to consider concerns/problems.

#### Establish a 'buffer zone' before going to bed

Set aside 90 minutes to engage in sedentary/relaxing activities; lights should be dimmed, stimulants should be avoided.

#### Use your bedroom only for sleep (and sexual intercourse)

Bed-bound patients require as much cognitive/physical stimulation as possible during daytime.

#### Go to bed only when sleepy

#### Get up if still awake after 20–30 minutes (and go back to bed only when sleepy)

Repeat the establishment of a 'buffer zone'.

#### Restrict napping

Avoid multiple naps, and naps in the evening.

A short nap in the afternoon 'may' be helpful, ie less than 1 hour, before 3–4pm.

#### Additional strategies

Minimise ambient light and noise; consider using eye masks and earplugs.

Adapted from Howell D, Oliver TK, Keller-Olaman S *et al*. *A pan-Canadian practice guideline: Prevention, screening, assessment and treatment of sleep disturbances in adults with cancer*. Toronto: Canadian Partnership Against Cancer (Cancer Journey Advisory Group) and the Canadian Association of Psychosocial Oncology, 2012.

### Box 3. Recommendations on use of pharmacological interventions for sleep disturbance.<sup>14,15</sup>

Management of sleep disturbance should focus on treatment of perpetuating factors, sleep hygiene and non-pharmacological interventions.

Medication should be restricted to patients with distressing sleep disturbance.

The choice of medication depends on a variety of factors, including patient-related factors (eg age, co-morbidities), clinical features (eg sleep pattern, associated symptoms) and drug-related factors (eg duration of action, side effect profile).

Medication should be prescribed for short periods (generally 1 week, maximum 3 weeks).<sup>a</sup>

Medication should be prescribed for intermittent usage (not continuous usage).<sup>a</sup>

Patients with difficulty initiating sleep (and in whom daytime sedation is undesirable) should be prescribed drugs with a short duration of action eg temazepam, zopiclone.

Patients with difficulty maintaining sleep (and in whom daytime sedation is acceptable) should be prescribed drugs with a long duration of action eg flurazepam, nitrazepam.

Benzodiazepines and the Z-drugs<sup>b</sup> should be avoided in the elderly due to potential side effects (eg confusion, falls).

Benzodiazepines and other hypnotics should be used with caution in patients receiving opioid analgesics due to potential side effects (eg sedation, respiratory depression).

Benzodiazepines (and the Z-drugs) cause physical/psychological dependence, and are associated with clinically significant withdrawal reactions (which can occur up to 3 weeks later).

a = tolerance develops within 3–14 days of continuous usage.

b = zolpidem tartrate, zopiclone.

be common in patients with advanced cancer (34.5% in the previous month).<sup>5</sup> Other investigators have reported an even higher prevalence in this population.<sup>7</sup> Vivid dreams are associated with sleep disturbance,<sup>5</sup> which increases the risk of waking up during REM sleep (which is the sleep stage primarily associated with dreaming). Vivid dreams are also associated with a higher psychological symptom burden,<sup>5</sup> which itself is associated with sleep disturbance.<sup>11</sup> However, vivid dreams do not appear to be more common with worse performance status (a surrogate for worse prognosis), and were not associated with the use of opioid analgesics in an observational study of 174 patients with advanced cancer.<sup>5</sup>

Patients reporting vivid dreams should be assessed for underlying sleep disturbance and/or psychological problems, and these should be appropriately managed (the management of sleep disturbance is discussed in the previous section). Specific treatment is invariably not required, although patients may require reassurance about the significance of the vivid dreams.

### Nightmares

Nightmares appear to be common in patients with advanced cancer (18% in the previous month),<sup>5</sup> although not necessarily

more common than in the general population.<sup>18</sup> Nightmares are associated with sleep disturbance in the general population,<sup>19</sup> and in patients with advanced cancer,<sup>5</sup> and it has been suggested that the sleep disturbance precipitates (recall of) the nightmares, rather than the nightmares precipitating the sleep disturbance.<sup>20</sup> Nightmares are associated higher physical and psychological burden,<sup>5</sup> which themselves are associated with sleep disturbance.<sup>11</sup> However, nightmares do not appear to be associated with the use of opioid analgesics in two observational studies of 297 patients with advanced cancer (or a review of opioid adverse effects),<sup>5,21,22</sup> although there are a number of other drugs that can precipitate nightmares (eg sedatives/hypnotics, beta blockers, amphetamines, dopamine agonists).

Patients reporting nightmares should be assessed for underlying sleep disturbance and/or physical and psychological problems, and these should be appropriately managed. Specific treatment is generally not required, but in those cases that meet the diagnostic criteria for 'nightmare disorder' (ie related/specific sleep disorder), recommended treatments include specific behavioural and psychological interventions (eg image rehearsal therapy, cognitive behavioural therapy), and specific pharmacological interventions (eg nitrazepam, prazosin).<sup>23</sup>

### Conclusion

Sleep disorders are common in patients with advanced disease, and are associated with significant morbidity in these groups of patients. Healthcare professionals should routinely screen for sleep disorders in patients with advanced disease, since many are amenable to simple interventions (with a resultant improvement in health-related quality of life). ■

### References

- 1 American Sleep Association, 2019. [www.sleepassociation.org](http://www.sleepassociation.org) [Accessed 14 April 2019].
- 2 Mystakidou K, Panagiotou I, Parpa E, Tsilika E. Sleep disorders. In: Cherny NI, Fallon MT, Kaasa S, Portenoy RK, Currow DC (eds). *Oxford Textbook of Palliative Medicine*, 5th edn. Oxford: Oxford University Press, 2015.
- 3 Zucconi M, Ferri R. Classification of sleep disorders. In: Bassetti CL, Dogan Z, Peigneux P (eds). *Sleep Medicine Textbook*. Regensburg: European Sleep Research Society, 2014.
- 4 Cheatle MD, Webster LR. Opioid therapy and sleep disorders: risks and mitigation strategies. *Pain Med* 2015;16:522–6.
- 5 Davies AN, Patel SD, Gregory A, Lee B. Observational study of sleep disturbance in advanced cancer. *BMJ Support Palliat Care* 2017;7:435–40.
- 6 Yennurajalingam S, Balachandran D, Pedraza Cardozo SL *et al*. Patient-reported sleep disturbance in advanced cancer: frequency, predictors and screening performance of the Edmonton Symptom Assessment System sleep item. *BMJ Support Palliat Care* 2017;7:274–80.
- 7 Gibbins J, McCoubrie R, Kendrick AH *et al*. Sleep-wake disturbances in patients with advanced cancer and their family carers. *J Pain Symptom Manage* 2009;38:860–70.
- 8 Dobing S, Frolova N, McAlister F, Ringrose J. Sleep quality and factors influencing self-reported sleep duration and quality in the general internal medicine inpatient population. *PLoS One* 2016;11:e0156735.
- 9 Maltby KF, Sanderson CR, Lobb EA, Phillips JL. Sleep disturbances in caregivers of patients with advanced cancer: a systematic review. *Palliat Support Care* 2017;15:125–40.

- 10 Hugel H, Ellershaw JE, Cook L *et al*. The prevalence, key causes and management of insomnia in palliative care patients. *J Pain Symptom Manage* 2004;27:316–21.
- 11 Graci G. Pathogenesis and management of cancer-related insomnia. *J Support Oncol* 2005;3:349–59.
- 12 Dong ST, Butow PN, Costa DS, Lovell MR. Symptom clusters in patients with advanced cancer: a systematic review of observational studies. *J Pain Symptom Manage* 2014;48:411–50.
- 13 Slatore CG, Goy ER, O'Hearn DJ *et al*. Sleep quality and its association with delirium among veterans enrolled in hospice. *Am J Geriatr Psychiatry* 2012;20:317–26.
- 14 Lis CG, Gupta D, Grutsch JF. The relationship between insomnia and patient satisfaction with quality of life in cancer. *Support Care Cancer* 2008;16:261–6.
- 15 Innominato PF, Spiegel D, Ulusakarya A *et al*. Subjective sleep and overall survival in chemotherapy-naive patients with metastatic colorectal cancer. *Sleep Med* 2015;16:391–8.
- 16 Howell D, Oliver TK, Keller-Olaman S *et al*. *A pan-Canadian practice guideline: Prevention, screening, assessment and treatment of sleep disturbances in adults with cancer*. Toronto: Canadian Partnership Against Cancer (Cancer Journey Advisory Group) and the Canadian Association of Psychosocial Oncology, 2012.
- 17 British National Formulary, 2019. <https://bnf.nice.org.uk> [Accessed 15 February 2019].
- 18 Bjorvatn B, Gronli J, Pallesen S. Prevalence of different parasomnias in the general population. *Sleep Medicine* 2010;11:1031–4.
- 19 Schredl M. Characteristics and contents of dreams. *Int Rev Neurobiol* 2010;92:135–54.
- 20 Simor P, Horvath K, Gombos F, Takacs KP, Bodizs R. Disturbed dreaming and sleep quality: altered sleep architecture in subjects with frequent nightmares. *Eur Arch Psychiatry Clin Neurosci* 2012;262:687–96.
- 21 Mercadante S, Girelli D, Casuccio A. Sleep disorders in advanced cancer patients: prevalence and factors associated. *Support Care Cancer* 2004;12:355–9.
- 22 Vella-Brincat J, Macleod AD. Adverse effects of opioids on the central nervous systems of palliative care patients. *J Pain Palliat Care Pharmacother* 2007;21:15–25.
- 23 Morgenthaler TI, Auerbach S, Casey KR *et al*. Position paper for the treatment of nightmare disorder in adults: an American Academy of Sleep Medicine position paper. *J Clin Sleep Med* 2018;14:1041–55.

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