

Insomnia in Palliative care

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Introduction

Sleep is a basic human need. Over the last few decades, there has been a significant growth in our knowledge and understanding about sleep. Sleep problems are common in patients with chronic illnesses such as cancer. Clinicians and patients tend to consider poor sleep as inevitable in the context of a chronic or advanced illness. Furthermore, many patients fail to alert their physicians of their problem because their concerns may have never been addressed or previously dismissed as being an inevitable part of a terminal illness. Not surprisingly the sleep problems of these patients go unrecognized or untreated.

The following covers a brief review on normal sleep and sleep regulation, discusses factors that lead to insomnia, presents the approach to a palliative care patient with insomnia, and concludes with a discussion on some of the interventions to promote sleep. The aim is to help the reader gain a broader understanding of this common palliative care problem.

Case Presentation

The following case histories reflect commonly encountered patients in a palliative care setting.

Case 1

Mr. Chan, a 64 year old gentleman, suffering from cancer of the sigmoid colon with liver metastases, was receiving palliative care as an in-patient. He suffered from persistent right upper quadrant pain, which was suboptimally controlled despite regular doses of morphine. He also complained of poor sleep during the course of his hospitalization. He had no difficulties initiating sleep but suffered from fragmented sleep, which left him feeling unrefreshed in the mornings. As an in-patient, he remained relatively inactive and frequently napped during the day. The usual hospital environment and routines were also contributing

to his poor sleep at night. His regular dose of morphine was escalated to improve pain control, and the hospital routines were reduced to a minimum. He was encouraged to remain active during the day. From the case history, it becomes clear that several mediating factors contributed to his sleep disturbance, correction of which, helped improve his sleep.

Case 2

Mrs. Lam, a 53 year old lady, suffering from cancer of the lung with intrapulmonary and lymph node metastases was referred to our Palliative care unit as an out-patient. She remained relatively well except feeling unrefreshed in the mornings despite having spent hours in bed at night. A detailed history showed that the culprit was Dexamethasone 4mg BD. Her previous history, as to why she was on steroids, was unclear. The steroids were gradually tailed down and then stopped, which helped improve her sleep.

Sleep and its mechanisms: an introduction

Sleep is no luxury, but an essential human need. Sleep is important for immune, endocrine and metabolic functions. Qualitatively or quantitatively deficient sleep affects health and well-being¹.

Sleep follows a circadian rhythm, regulated by environmental and biohumoral factors². Melatonin, produced from pineal gland, is produced in the night and involved in the sleep-wake cycle. Sleep consists of rapid-eye-movement (REM) and non-rapid-eye-movement (NREM) states. The REM state has been depicted as a "highly activated brain in a paralyzed body", consisting of dreams, EEG activity, muscle atonia and autonomic variabilities. The NREM state has been depicted as a "relatively inactive brain in a movable body", where EEG activity slows, and voluntary muscle control and tone remain intact. Each cycle, including both REM and NREM stages, lasts about 90 minutes and there are about 4 to 6 such cycles for 7 to 8 hours of sleep¹.

Insomnia - definition

Insomnia represents a subjective complaint of poor sleep³. It encompasses both quantitative and qualitative sleep problems including those of insufficient sleep hours, fragmented sleep, prolonged sleep latency, non-restorative sleep and sleep during the wrong time of the circadian rhythm.

Insomnia is a symptom and not a diagnosis, and warrants a detailed history. Insomnia means different things to different patients. As there is no gold standard definition of normal sleep, insomnia becomes difficult to define and measure. In clinical practice, it is the patients' subjective complaint of impaired sleep quality and/or quantity which is the most important.

Prevalence of insomnia in cancer

Sleep disturbances are common in cancer patients. Estimated prevalence of sleep disturbances in cancer patients vary widely ranging from 24% to 95%.⁴ Prevalence estimates vary significantly because of differences in the adopted definition, the measurement tool used and the specified time frame in which it was measured.

According to a cross-sectional study by Davidson et al⁵ involving a heterogenous group of 982 cancer patients, the estimated prevalence of insomnia in the previous 4 weeks was 31%. The estimated prevalence of insomnia in another cross-sectional study by Hugel et al⁶ conducted on 74 patients receiving palliative care was 70%.

Factors contributing to disturbed sleep

Disturbed sleep is usually the result of multiple factors, some reversible and others not. Some physical, psychological and lifestyle factors precipitate sleep disturbances.

1. Physical factors

Uncontrolled physical symptoms such as pain, nausea/vomiting, dyspnea, urinary frequency are amongst the many physical symptoms that can contribute to disturbed sleep. Helping patients alleviate their physical symptoms can improve sleep quality. In a cross-sectional study by Hugel et al including 74 in-patient palliative care patients, 60% of patients with insomnia attributed uncontrolled physical symptoms to their sleep disturbance⁶.

2. Psychological factors

Symptoms such as anxiety and depression can affect sleep quality, but can also be the result of poor sleep. It is important to obtain a detailed history to assess for such psychological symptoms. In a descriptive study involving 123 advanced cancer in-patients at a Palliative care unit, using a questionnaire and nonstructured interview, Mercadante et al concluded that patients who reportedly felt anxious and depressed had less restoring sleep and more nightmares⁴.

3. Behavioral factors¹

Many hospitalized patients tend to remain relatively inactive during the day or take frequent day-time naps which disturbs the sleep-wake cycle.

4. Cognitive factors

In the cross-sectional study by Davidson et al⁵ on a heterogenous group of cancer out-patients, the authors reported that 52% patients felt that their thoughts contributed to poor sleep. Concerns about their personal health, and concerns about their families or friends also contributed to sleep disturbances.

5. Drugs

Many concomitant drugs that patients are taking have arousing properties that interfere with sleep and those used commonly in palliative care include steroids and psychostimulants¹. Davidson et al reported that cancer treatment in the previous 6 months including surgery, chemotherapy or radiation therapy contributed to sleep disturbances⁵.

6. Emotional factors⁷

Going to bed with negative emotions such as fear and anger can impair sleep. Psychiatric problems e.g. anxiety and depression can present as sleep problems.

7. Environmental factors

A typical acute hospital environment creates further disturbances to patients' sleep-wake cycle. The noise from beeping machines and lights, some drug treatment schedules such as 4-hourly medications, and hospital routines such as blood pressure taking, also contribute in affecting the patients' quality and quantity of sleep.

Onset of the problem

In the paper by Hugel et al⁶, 75% of patients suffering from insomnia developed the problem after their diagnosis of cancer. In a separate study⁵ involving cancer patients, 48% of those patients reported to be suffering from insomnia reported that their symptom onset occurred around the time of their cancer diagnosis (6 months pre-diagnosis to 18 months post-diagnosis). Some cases of insomnia have existed way before the cancer diagnosis; further emphasizing the importance of a detailed history.

Impact of insomnia

Insomnia can impact patients significantly in the physical, psychological, cognitive and social realms. In the cross-sectional study by Davidson et al⁵ involving 982 cancer patients, 31% had insomnia. Among patients with insomnia, 89% of them felt that their sleep disturbance affected how they felt physically; 76.3% indicated that the sleep trouble affected their ability to cope with stress; 72.3% indicated that it affected their emotions; 65% felt it affected their ability to carry out usual activities; and 64.7% felt that it affected their ability to concentrate.

The sleep of family members, especially those who are caregivers for the chronically and terminally ill, is also at risk for being disrupted or inadequate due to either the patients' sleep problems or the burdens of care-giving^{8,9}.

Tools to aid assessment

There are various tools, some which offer an objective assessment, and others subjective¹.

In objective assessment, the polysomnography is the gold standard tool for sleep assessment as recommended by the American Sleep Disorders Association (ASDA)¹. It is inclusive of an electroencephalography, electrocardiography, and electromyography assessment. It can be conducted either in the hospital or in a home-setting. However, polysomnographic testing can prove burdensome on patients receiving palliative care.

Subjective assessment tools include sleep quality questionnaires (e.g. Pittsburg Sleep Quality Index PSQI), use of sleep diaries (e.g. National Sleep Foundation Sleep Diary NSFSD;

Pittsburg Sleep Diary PSD) and daytime sleepiness inventories (e.g. Epworth Sleepiness Scale ESS)¹.

Approach to insomnia in palliative care

There is a growing body of evidence showing the impact of sleep disturbances on patients. It is important that we as members of the palliative care team regularly assess for disturbances in quality or quantity of sleep. Although various objective and subjective measures of sleep are available, an initial assessment relies on subjective information, first-hand, from our patients.

Some important points that need to be covered in a thorough history include:

1. What does the patient specifically mean by poor sleep?
2. Evaluate 24 hour sleep-wake cycle
3. Look for reversible causes/mediating factors that contribute to sleep disturbances
4. Detailed drug history
5. Consumption of caffeine/alcohol
6. Previous treatment tried for insomnia, including those which have been used with success, and those failed therapies
7. Impact of insomnia on patient/caregiver

Management of insomnia

1. Explore the impact of the problem and patients' expectations

The first step in management of insomnia is to explore its effects on the patient. As with the management of any other symptom in palliative care, it is important to explore the patients' expectation and realign them closer to reality if necessary. The ultimate aim is to allow for enough restorative sleep. What is enough for one patient may not be for another. So it is important to individualize management as per patients' requirements.

2. Reverse the reversible factors contributing to disturbed sleep where possible

The causes of sleep disturbances are often multifactorial. A detailed history helps evaluate the contributing factors. It is important to reverse these as far as possible before considering other interventions to improve sleep.

3. Interventions to improve sleep

Because sleep disturbances often result from a combination of factors, no single intervention is likely to be effective universally. Often a combination of pharmacological and non-pharmacological interventions is warranted. Non-pharmacological options include emphasis on sleep hygiene and behavioral interventions. Various pharmacological options are available - some as prescription drugs; whereas others can be purchased over the counter.

Sleep Hygiene

Sleep promoting behaviors can be reinforced in all patients. Though simple and easily followed, these day-to-day measures have not been tested for efficacy in managing insomnia. The following 10 tips have been recommended by the American Sleep Association (ASA)¹⁰:

1. Maintain a regular sleep routine
2. Avoid naps if possible
3. Do not stay in bed awake for more than 5-10 minutes
4. Do not drink caffeine inappropriately
5. Do not watch TV or read in bed
6. Avoid substance that interferes with sleep
7. Exercise regularly
8. Have a quiet, comfortable bedroom
9. If you are a "clock watcher" at night, hide the clock
10. Have a comfortable pre-bedtime routine

Behavioral interventions

Different interventions have different levels of evidence. Common types studied in cancer patients include hypnosis, imagery training, muscle relaxation, stimulus control and multimodal interventions¹¹. These various interventions have resulted in subjective and/or objective improvement in sleep.

Pharmacological interventions^{1,12,13}

When non-pharmacological interventions alone do not resolve sleep problems, the addition of medications are usually warranted. Drugs commonly used in the management of sleep disturbances include the benzodiazepine group of drugs (BDZ), benzodiazepine-like drugs, sedating antidepressants, sedating antihistamines and melatonin. In our local setting, herbal mixtures with hypnotic properties are also available over the counter e.g. Suanzaorentang 酸棗仁湯¹⁵.

1. Benzodiazepine and Benzodiazepine-like group

The BDZs produce exert their effect by binding to the gamma-aminobutyric acid (GABA)-benzodiazepine receptor complex without displacing GABA. The drug binds to its specific attachment site and improves GABA's attraction to its own receptor site on the GABA-benzodiazepine receptor complex. Other than for their sedative effects, this group of drugs is commonly used in palliative care for their anti-convulsant properties. They improve sleep by decreasing sleep latency, reducing awakenings, increasing total sleep and imparting a sense of refreshing sleep.

Because longer term studies assessing the adverse effects of prolonged use of such drugs are lacking, the BDZs are recommended only for short term use, ideally for a period of less than 4 weeks.

The UK Committee on the Safety of Medicines (UK-CSM) has put forth recommendations for the use of BDZ group of drugs in insomnia¹⁵. These include the use of these drugs only when insomnia is causing considerable distress. The lowest dose being recommended for the shortest duration possible (i.e. less than 4 weeks), after which the dose must be tapered gradually and stopped. There is a risk of tolerances, physical dependence and psychological dependence developing with prolonged use. Patients also need to be monitored for side effects. However, limiting the use of these drugs to a period of less than 4 weeks in a palliative care setting has raised some concerns. Because the life expectancy of palliative care patients is usually short, the time restriction (i.e. use of BDZ for less than 4 weeks) is sometimes ignored and BDZs are used for longer durations. However, this practice is controversial.

Intermediate acting BDZs are preferred. Longer acting drugs with active metabolites especially in the elderly or those with altered liver function can pose significant problems, where the sedative effects are especially prolonged causing excessive drowsiness or dizziness the following day. Short acting drugs with inactive metabolites can also pose problems because the sedative effects are time limited, resulting in insufficient rest or sleep.

Adverse effects include nausea and vomiting, cognitive changes (including decreased attention span, impaired concentration and memory retrieval) and impaired psychomotor functioning such as impaired coordination and balance.

BDZs need to be used cautiously especially when combined with opioids in palliative care, with a risk of increased drowsiness and confusion. One needs to be cautious when using such drugs in the elderly because of paradoxical agitation, risk of falls and cognitive impairment.

The BDZ-like group of drugs includes Zopiclone, Zolpidem and Zaleplon. These selectively bind to type 1 benzodiazepine receptors in the CNS. Unlike the BDZ group of drugs, BDZ-like drugs do not have anxiolytic nor anticonvulsant properties. They are better tolerated and safer for use in the elderly. They improve insomnia by diminishing sleep latency (Zolpidem, Zopiclone and Zaleplon) and reducing nocturnal awakenings (Zopiclone).

A meta-analysis conducted by Nowell et al¹⁶ including 22 randomized placebo-controlled trials with a total of 1894 patients with chronic primary insomnia concluded that the use of Benzodiazepine group of medications or Zolpidem was significantly more effective than placebo in reducing sleep latency, reducing the number of awakenings, increasing total sleep time and improving sleep quality. On the contrary, research on the use of these drugs in cancer or palliative care patients, is lacking. As such, a review by the Cochrane¹⁷ collaboration concluded that there was no evidence from randomized controlled trials to help draw any conclusions regarding the use of benzodiazepines in palliative care.

2. Sedating Antidepressants

Some examples of sedating antidepressants include Amitriptyline, Mianserin and Doxepin. This group of medications is a useful option for depressed patients with insomnia. The hypnotic dose used is lower than the recommended dose to manage depression. The Selective Serotonin Receptor Inhibitor (SSRI) group of antidepressants (e.g. Fluoxetine, Sertraline) is more stimulating and is likely to cause insomnia if taken close to bedtime. Because there is little evidence to establish the efficacy and safety of

these drugs in nondepressed insomniacs, this group of medications is not recommended as the first line treatment for insomnia.

3. Sedating Antihistamines

Examples of antihistamines producing drowsiness include Chlorpheniramine and Diphenhydramine. Similar to the previous group, efficacy and safety of antihistamines for use as hypnotics has not been well established. Because of the absence of well-established evidence supporting their use in insomnia and the possible adverse effects such as psychomotor and cognitive impairment, antihistamines are not recommended for management of insomnia.

4. Melatonin

A naturally occurring hormone produced by the pineal gland at night, melatonin is widely available in over the counter preparations. A local study¹⁴ on over the counter sleeping pills reported that melatonin was found in 5 out of 17 preparations. There is conflicting evidence supporting its use as a hypnotic. However, there are concerns on possible contaminants in the melatonin manufacturing process causing hypersensitivity reactions. Up to date, there are no large scale controlled trials that provide data on long term safety and efficacy to support the use of Melatonin for the symptomatic management of insomnia in palliative care patients.

5. Herbal mixtures

One of the most commonly available over-the-counter sleeping pills in a local survey¹⁴ was the Chinese herbal mixture Suanzaorentang 酸棗仁湯. A study by Chen et al¹⁸ reported that this herbal mixture helped improve sleep quality in comparison to patients receiving placebo.

Summary

Insomnia is a symptom, and not a diagnosis per-se. Poor sleep means different things to different people. Numerous mediating factors contribute to disturbed sleep, which need to be reversed where feasible. If these fail, pharmacological and non-pharmacological measures should be initiated early to reduce the impact of poor sleep on both patients and their caregivers.

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Two Patients with Hypoglycaemia

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Recurrent hypoglycemia is not uncommon in palliative care patients. Ideally, treatment should be targeted at the underlying causes. In palliative care setting, some of the underlying causes may not be reversible and thus hypoglycaemia is treated symptomatically. Treatment can be given via intravenous or oral route. As long term dextrose infusion has the disadvantages of being more invasive and inconvenient for patient, per oral treatment may be a better option. The following cases illustrate two causes of recurrent hypoglycaemia in advanced cancer and their treatment.

Case history 1

Madam X was a 90-year-old, old age home (OAH) resident and was partially dependent in her daily activities. She had history of recurrent hypoglycaemia and suspected to have insulinoma around 15 years ago. She was advised to have more frequent carbohydrate intake at that time. Investigations performed in April 2006 showed an insulin level of 28 H and C-peptide of 1.86 H.

She was admitted to Queen Mary Hospital (QMH) in Dec 2006 for increased frequency of hypoglycemic attacks in OAH, manifested as agitation and irrelevant speech. Her random blood glucose on admission was 1.4mmol/l.

Despite dextrose infusion, she continued to have frequent hypoglycemia, ranging from 1.8-2.8mmol/l. Diazoxide was given orally and titrated against clinical response. The dosage was stepped up to 100mg tid and her condition improved. Her agitation and confusion subsided and blood sugar was maintained in the range of 9-15mmol/l.

Case history 2

A 79-year-old woman was diagnosed to have metastatic carcinoma of rectum in May 2007. There was multiple lung and liver metastasis with gross hepatomegaly. She was admitted to QMH for drowsiness and bleeding per rectal. The patient declined chemotherapy and radiotherapy. She developed recurrent hypoglycaemia requiring constant dextrose infusion. She was later transferred to our unit for pain control. As her hypoglycaemia persisted (lowest blood sugar at 1.2mmol/l), finding intravenous (IV) access became difficult with prolonged dextrose infusion. As non-islet cell tumour hypoglycaemia (NICTH) was suspected clinically, dexamethasone 4mg was given orally. Subsequently, there was no recurrence of hypoglycaemia and no further intravenous dextrose solution was needed. She died peacefully eventually.