

RESEARCH ARTICLE

Insomnia in Cancer - Associations and Implications

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Abstract

Background: Insomnia is a common condition in cancer patients. In spite of the high prevalence its associations have not been well studied. Existing data suggests that insomnia is related to depression and pain. However, the impact of ongoing chemotherapy on sleep is not investigated. **Aim:** To study the relationship between insomnia and chemotherapy after analysing confounding variables. **Materials and Methods:** Consecutive patients who visited New England Oncology Clinic in Tamworth were recruited. Insomnia was assessed with the Bergen insomnia scale. The Montgomery Asberg Depression rating scale was used to measure depression. Pain was assessed with the Brief Pain inventory. Chronic medical conditions, type of cancer, side effects to chemotherapy, role of steroids and other drugs were studied as confounders. **Results:** A total of 56 patients participated in the study. Age ranged from 33 to 83 years (mean: 63.6, SD=10.97). There were 29 men and 27 women. 42 patients received at least one form of chemotherapy and 15 were receiving radiotherapy at the time of assessment. Mean insomnia score was significantly higher in those receiving chemotherapy than in those without chemotherapy (8.92 vs 17.2, two tailed $p=0.005$, 95% CI=2.63-13.71). There was no significant variation in insomnia scores in terms of chronic medical condition, type of cancer, psychiatric history, use of steroids or adverse effects of chemotherapy. However, total insomnia score was correlated with depression rating score (Pearson correlation, $r=0.39$, $p=0.003$) and magnitude of pain ($r=0.37$, $p=0.006$). On regression analysis only pain was found to be predictive of insomnia. **Conclusions:** Insomnia in patients with cancer is found to be associated with concurrent chemotherapy and correlated with degree of depression and pain. Identifying factors related to insomnia in cancer population has implications in its management and patient education.

Keywords: Insomnia - chemotherapy - depression - pain - management

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Introduction

Adequate sleep is an essential component of quality of life. Insomnia is a sleep disorder characterized by trouble falling sleep, staying asleep or waking up too early (Punnoose et al., 2012). The prevalence of insomnia varies. According to the criteria of Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR) (American Psychiatric Association., 1994), the point prevalence of insomnia has been estimated as 6% (Ohayon et al., 1997). Sleep disturbances are associated with various chronic medical conditions notably cardiovascular, pulmonary and rheumatic diseases (Gilsason et al., 1993; Foley et al., 1995; Katz et al., 1998). Psychiatric disorders including depression are strongly linked to insomnia (Katz et al., 1998).

Pain and depression are highly prevalent in patients with cancer and are associated with insomnia. Pooled data shows more than 50% prevalence of pain when all types of cancers are included (Beuken et al., 2007). A systematic review found that prevalence of depression in cancer varied from 4% to 49% according to the treatment settings

(Walker et al., 2013) and another meta-analysis concluded a pooled prevalence of 16% (Mictell et al., 2011). Various studies show that sleep disturbance is a common complaint in patients with pain and half of all patients presenting with insomnia suffer from chronic pain (Smith et al., 2004; Tang et al., 2007; Taylor et al., 2007). Sleep changes are part of depressive syndrome and the criteria for a diagnosis of depression (American Psychiatric Association., 2013). For these reasons understanding insomnia in cancer patients is a great challenge. There is no information on the impact of chemotherapeutic agents on insomnia. The present study investigated the role of chemotherapy in insomnia. Existing but limited data indicates an insomnia prevalence of 31% in cancer patients (Davidson et al., 2002). A recent study found that 40% patients with cancers have poor sleep quality (Akman et al., 2015).

Since the relation of insomnia with pain, depression and chronic medical conditions and common prevalence of these conditions in cancer, the investigation of insomnia in the presence of these factors becomes very complex. We therefore studied insomnia in cancer patients in the present study after controlling all known confounders of insomnia.

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Materials and Methods

This was a prospective study where participants were recruited from the North West Cancer Centre within the New England Health Service. The local institutional board reviewed the ethical aspects and approved the study. Each participant consented to give relevant information and complete questionnaires. The Bergan Insomnia Scale assessed sleep. This scale has been validated among community residents and patients and is one of the few instruments that is validated against subjective as well as polysomnographic data (Pallesen et al., 2008). The test-retest reliability has been estimated as 0.77. The Brief Pain Inventory was used to assess pain. This instrument was originally developed to study pain in cancer patients. We used Montgomery-Asberg Depression Rating Scale for the assessment of depression. Quality of life was assessed by Quality of Life scale (QOL).

Analysis was done using independent 't' test to compare the Bergan insomnia rating score between patients receiving chemotherapy and those without chemotherapy. Comparison was also done in reference to other variables, viz., presence of chronic medical conditions, use of steroids and hypnotics, type of malignancy, radiation therapy and adverse effects of chemotherapy. Pearson's correlation test was utilized to examine correlation between depression and insomnia, pain and insomnia and QOL and insomnia. Finally regression analyses were done with insomnia score as a dependent variable and factors that were associated and correlated with insomnia as independent variables.

Results

This was a prospective study at an outpatient oncology clinic that involved consecutive samples. 56 patients participated in the study. Age ranged from 33 years to

Table 1. Participants' Characteristics

Total participants	56
Age range	33 to 83 (mean=63.6, SD=10.97)
Gender	Females, n=27, males, n=29
Number of patients with chemotherapy	42
Radiotherapy	15
Number of patients with chronic medical conditions	21
Psychiatric illnesses	11
Number of patients who used sleeping medication	13

Table 2. Cancer Frequency

	Frequency	Percent
Colon	18	32.1
Ovary	2	3.6
Breast	8	14.3
Lung	12	21.4
Testicular	1	1.8
Pancreas	3	5.4
Melanoma	1	1.8
Prostate	7	12.5
Others	4	7.2
Total	56	100

83 years (mean: 63.6, SD=10.97). There were 29 men and 27 women. 42 patients received at least one form of chemotherapy and 15 were receiving radiotherapy at the time of assessment. One or more chronic medical condition was present in 21 patients and 11 had a psychiatric illness. 37 patients were taking steroids and 13 were on sleeping medications. The participants' characteristics are given in Table 1.

The most common cancer was that of colon (n=18) followed by lung cancer (n=12) and breast (n=8). Frequency of other cancers is given in Table 2. The most commonly used chemotherapeutic agents were Capecitabine or Capecitabine and Oxaliplatin (see Table 3). 25 patients had targeted chemotherapy and Avastin was the most common agent (Table 4).

The mean insomnia score for the whole sample was 15.16 (SD=11.55). There was a difference in insomnia score between the group of patients who did not have chemotherapy (8.92, SD=7.2) and those who had one or more chemotherapeutic drugs (17.10, SD=12.01). This difference was significant at 95% confidence interval (p=0.005, CI=2.63-13.71). The insomnia score was also high in patients who had radiotherapy (17.08 vs 10.08, p=0.017, CI=1.33=12.68). However, insomnia score did not differ significantly in reference to presence of a chronic medical condition, psychiatric disorder, side effects of chemotherapy, use of analgesic medication, hypnotics or steroids. 13 patients were using one or more hypnotic medications and they scored less on insomnia scale, but their insomnia score did not significantly differ from those without sleeping medications.

Pearson correlation test revealed significant positive correlation between insomnia score and depression score (r=0.39, p=0.003) and insomnia and pain score

Table 3. Chemotherapy Type

	Frequency	Percent	Valid Percent
Capecitabine/Oxaliplatin	7	12.5	12.5
5 Fluorouracil	1	1.8	1.8
Others	5	8.9	8.9
No chemotherapy	13	23.2	23.2
Capecitabine	7	12.5	12.5
5 Fluorouracil/ Oxaliplatin	1	1.8	1.8
Platinum and Etoposide	5	8.9	8.9
Alimta	4	7.1	7.1
Taxol	4	7.1	7.1
5 Fluorouracil/ Epirubicin/ Cyclophosphamide/ Docetaxel	2	3.6	3.6
5FU/Irinotecan	2	3.6	3.6
Gemcitabine/carboplatin	5	8.9	8.9
Total	56	100	100

Table 4. Targeted Chemotherapy Type

	Frequency	Percent
Avastin	11	19.6
Herceptin	4	7.1
Abiraterone	4	7.1
TKI	5	8.9
Others	2	3.6
No	30	53.6
Total	56	100

Table 5. Multiple Linear Regression Analysis

Model		Standardized Coefficients Beta	Sig.	95.0% Confidence Interval	
				Lower Bound	Upper Bound
1	(Constant)		0.004	2.562	13.161
	MADRS	0.299	0.026	0.076	1.169
	Pain	0.266	0.047	0.002	0.248

($r=0.37$, $p=0.006$). In addition, there was significant inverse correlation between insomnia and QOL ($r=0.325$, $p=0.016$). There was no significant correlation between insomnia score and age. When we did multiple linear regression analysis the significance of pain and depression remained (table 5). However, on nominal regression analysis where chemotherapy was entered as nominal and independent variable and insomnia as dependent variables with pain and depression as co-variates only pain was found to be significant predictor of insomnia.

Discussion

In this study, we attempted to examine the association between insomnia and chemotherapy in patients with malignancy. It has been shown that Insomnia is a common problem in cancer patients (Davidson et al., 2002; Akman et al., 2015). For example, a systematic review concluded that women with breast cancer tended to report higher levels of sleep disturbances upon receiving chemotherapy or radiotherapy (Costa et al., 2014). Here, our results also indicated that radiotherapy and chemotherapy are associated with insomnia in different types of cancers and our results are consistent with that of others (Savard et al., 2015). Nonetheless the relationship between insomnia and the commencement of chemotherapy is inconsistent. A prospective study in patients with non-small cell lung cancer has shown poor sleep quality before and during chemotherapy therapy suggesting that sleep disturbance is present regardless of chemotherapy (Dean et al., 2015).

Given the complexity of factors present in cancer and their relation to insomnia this is unsurprising. One explanation is that chemotherapy is one of the factors associated with insomnia. On the other hand, we illustrated that insomnia is correlated with severity of depression and pain. Although patients with chemotherapy had a significantly higher score of insomnia, it did not retain significance in linear regression model when controlled for depression and pain. It is also important to note that it was chemotherapy, not side effects of chemotherapy, chronic medical conditions or use of steroids that was associated with insomnia. Interestingly the presence of a psychiatric disorder was not associated with insomnia, but at the same time insomnia was positively correlated with depression severity. This implies that undiagnosed depression may be contributing to insomnia in cancer patients. Similarly the use of analgesics or sleeping medication was not associated with significant reduction in insomnia score. This finding although reported previously (Zhao et al., 2013), is unexpected and is probably reflective of the fact that doses or types of these medications were insufficient to improve pain and sleep. However, this is consistent with the observation that sleep disturbance in cancer patients

are under-recognized and even when they are recognized they remain undertreated (Dahiya et al., 2013).

We have established that insomnia is negatively correlated with QOL. These findings have been reported elsewhere (Clevenger et al., 2013; Nishiura et al., 2014). We have replicated the finding that sleep disturbance were not associated with age, but with pain and depression (Davis et al., 2014). Previous findings suggested that glucocorticoids were associated with sleep disturbances in cancer patients (Zhao et al., 2013), but we did not find any association. This may be due to differences in sample population and differences in types and stages of cancers.

The current study is as it comprehensively investigated, comprehensively investigating the well-recognised factors that are involved in both insomnia and cancer. Our investigation is a real world study that included different types of cancers without any selection bias, from consecutive samples, and therefore the results of the study have more generalizability. It is noteworthy that this study was conducted in a rural setting where resources are limited and there are no clinics specialized for each type of cancer.

The limitations of the study include small sample size and absence of data prior to commencement of chemotherapy. For this reason we could not analyse impact of type of cancer or stages of cancer on insomnia. We did not study insomnia before, during and after chemotherapy. This limits conclusions regarding effect of chemotherapy on insomnia.

In conclusion, Insomnia in cancer patients is associated with chemotherapy, but not as an independent factor. Other factors, pain and depression are also correlated with insomnia. Pain is an independent predictor of insomnia in the given sample. Insomnia is correlated with poor quality of life. Use of analgesics or hypnotics is not associated with better sleep.

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