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Literature Review

Sleep Disturbance in Gynaecologic Malignancies-an Overview

Pavan Deepak*

Radiation Oncology Resident at JNMCH, Aligarh Muslim University, India

***Correspondence to:** Pavan Deepak; Radiation Oncology Resident at JNMCH, Aligarh Muslim University, India; Tel: +91-9176851924; E-mail: mvrpavandeepak@gmail.com

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LITERATURE REVIEW

Sleep plays a pivotal role in maintaining homeostasis and one of a few foremost determinants of Quality of Life. Quality of life is a well-studied topic in oncology and various measures are taken to improve quality of life in this setting, in order to achieve therapeutic outcome and compliance in general in cancer patients.

Sleep disturbances and disruption in circadian rhythm is among a few common presenting complaints of patients with malignancy and affects between 30% to 75% of newly diagnosed or recently treated cancer patients,[1] which are reported as double that of the general population, paving the way for decreased compliance and inefficacy of therapy and pose as a detriment to general well-being, and quality of life.

It is evident that mood disorders and sleep disturbances are more prevalent in females (1.3 to 1.8 times more than men),[2] one may theorize that the prevalence of sleep disturbance in gynaecologic malignancies is greater than that of general population.

Sleep disturbances in gynaecologic cancer patients often include difficulty in initiation of sleep, frequent awakening, difficulty in staying asleep, and restless leg syndrome.

Systematic research on various sleeps disorders and their therapeutic approach in gynaecologic cancers in general is lacking. This article aims at elucidating and giving overview of sleep pattern changes in gynaecologic malignancies and therapeutic approaches to foster better sleep in this subset of population. This article also emphasizes the need to envisage the treatment strategies targeting cytokines and cortisol in improvement of sleep parameters in gynaecologic malignancies.

DISCUSSION

Etiology

Various factors are implicated in sleep disturbances in patients with gynaecologic malignancies. Organic causes like Intense local site pain, ascites, abdominal discomfort, episodes of emesis, side effects of interventions viz., surgery (presence of drain tube), chemotherapy, radiotherapy and paralysis are some of the factors leading to sleep deprivation in patients with gynaecologic malignancy. Psychosocial factors include the stress of diagnosis itself that may contribute to anxiety and depression, financial constraints, inability to socialize.

Several studies have been attempted to understand the etiology and pathophysiology of sleep disturbance contributing to development of gynaecologic malignancies. Some studies notably that of M Cohen et al.[3] dwells on how pineal gland function affected the development of breast cancer. The brief pathophysiology according to the study was that melatonin inhibits ovarian estrogen production, pituitary gonadotrophin production, and sexual development and maturation. Study further observed that psychiatry drug Chlorpromazine increases serum-melatonin levels and reported that psychiatric patients taking chlorpromazine have a lower incidence of breast cancer.

High levels of proinflammatory cytokine IL-6 is often implicated in development of central vegetative symptoms including malaise, fatigue, sleep alterations and depression. Vgontzas et al.[4] suggested that good night's sleep is associated with decreased daytime secretion of IL-6 and that Sleep deprivation increases daytime IL-6 and causes somnolence and fatigue during the next day. Furthermore, it was observed by Susan K Lutgendorf et al.[5] that patients with ovarian cancer have higher levels of IL-6, contributing to these central vegetative symptoms.

Personal factors like work schedule, decreased libido, also play a role in the progression of malignancies by contributing to insomnia. Brian D Carter et al.[6] examined possible associations of three measures of circadian disruption: nontypical work schedules, nightly sleep duration, and monthly frequency of insomnia with risk of fatal ovarian cancer in 161,004 employed women in the American Cancer Society's Cancer Prevention Study–II, a cohort that has been followed for mortality from 1982 till 2010. After 28 years of follow-up, 1289 deaths from ovarian cancer occurred in the at-risk cohort. It was concluded that as compared to fixed daytime work, a rotating schedule was associated with an elevated risk of fatal ovarian cancer (RR=1.27, 95%

CI=1.03, 1.56). No association was established between insomnia and fatal outcomes.

Chemotherapy among treatment regimens may lead to significant toxicities paving the way for sleep disturbance. Wu and Lorizio et al.[7] concluded that women with higher levels of endoxifen, the most active metabolite of tamoxifen, were more likely to experience sleep disruption. In addition, 64% of women who were prescribed tamoxifen also experienced hot flashes, independently contributing to disturbed sleep.

Prevalence and Outcome

Several studies have been performed to inspect the sleep disruption prevalence in gynaecologic malignancies and analyse its effects on prognosis.

Lauren Clevenger et al.[8] demonstrated the association of depression and sleep disturbance in the setting of ovarian cancer. Greater increase in depression was associated with increased disturbances in sleep quality over time ($p<.04$). This study stratified patients based on three time points –pre-surgery, 6 months post-surgery and 1 year post-surgery. Disturbed global sleep (PSQI>5) at all three time-points were claimed by majority of patients. Medications for sleep and pain were found to be associated with worse sleep at all time-points. Worsening sleep was also associated with declines in QOL over time ($p<.001$).

A total of 76 stages I and II cervical cancer patients and 116 female residents completed the Pittsburgh Sleep Quality Index (PSQI) before and after adjuvant therapy in a study by Jun Tian et al.[9] and concluded that the prevalence of poor sleep quality in stages I and II cervical cancer patients was approximately twice than that of women in the communities (27.59 % for female residents, 52.63 % for patients before adjuvant therapy, and 64.50 % for patients after adjuvant therapy). Psychological distress, depression, anxiety, and high grade of CIPN during adjuvant therapy were factors associated with poor sleep quality. Exercise was found to be a protective factor for poor sleep quality ($P=0.019$).

Ann M. Berger et al.[10] conducted a RCT of 219 women with stage I–IIIA breast cancer who were randomized 2 days prior to starting chemotherapy to a behavioural therapy sleep intervention or healthy eating control group at three times: the start (Tx 1), continuation (Tx 3), and recovery (30 days after last Tx) of chemotherapy and sleep parameters were measured by wrist actigraphy for 7 days. Study observed that Circadian activity rhythm parameters at three times in both groups were disrupted compared to healthy adults, but similar to values of cancer patients.

Julie L Otte et al.[11] compared the sleep-wake disturbances in long-term breast cancer survivors (BCS) with age-matched women without breast cancer (WWC) based on Pittsburgh Sleep Quality Index (PSQI) scores. This study concluded that BCS had significantly more prevalent sleep-wake disturbances (65%) compared with WWC (55%) ($P<0.05$). BCS also had significantly higher PSQI global scores indicating poorer sleep quality compared with WWC ($P<0.05$).

Ninety-seven women with metastatic breast cancer participated in a study by Cheryl Koopman et al.[12] where sleep, depression symptoms, and social support were assessed. The study suggested that women with metastatic breast cancer who are at higher risk for having sleeping problems are those who are less educated, in pain, depressed, have bony metastases, or lack social support as most women (63%) reported one or more types of sleep disturbance and 37% reported using sleeping pills in the previous 30 days.(Table 1)

Table 1. These Studies are enlisted in a tabulated format

First Author	Participants	Results
Lauren Clevenger et al	Ovarian Cancer N:173	Majority of ovarian cancer patients had disturbed global sleep (PSQI >5)
Jun Tian et al	76 stages I and II cervical cancer patients and 116 female residents	Mean PSQI scores before adjuvant therapy- 3.814, $P<0.001$ After Adjuvant therapy-5.957, $P<0.001$ Prevalence rates of poor sleep quality were 27.59 % for female residents, 52.63 % for patients before adjuvant therapy, and 64.50 % for patients after adjuvant therapy.
Ann M. Berger et al	219 women with stage I–IIIA breast cancer	Circadian activity rhythm parameters at three times in both groups were disrupted in the breast cancer group.
Julie L.Otte et al	cross-sectional study of 246 BCS and 246 WWC	BCS had significantly more prevalent sleep-wake disturbances (65%) compared to WWC (55%) ($P<0.05$)
Cheryl Koopman et al	Metastatic Breast Cancer N- 97	CES-D total scores 6.86, $p<0.001$ women with metastatic breast cancer who are at higher risk for having sleeping problems are less educated, in pain, depressed, have bony metastases, or lack social support
N- Sample size; P- P value; CI- Confidence Interval PSQI- Pittsburgh Sleep Quality Index BCS- Breast Cancer Survivor, WWC- Women without Cancer CES-D- Centre for Epidemiologic Studies- Depression Scale		

Treatment

Timely treatment of organic causes of sleep disruption is the pivotal step. Prompt inclusion of antiemetics, analgesics, anti-depressants, sedative-hypnotics is necessary. Palliative treatment measures like Palliative radiotherapy for bone secondaries, Hemostatic radiotherapy for controlling excessive bleeding, etc must be taken to improve quality of life and to treat temporary problems that culminate in sleep disruption.

As sleep disturbances tend to be chronic impedance to cancer recovery, patients may often require chronic use of sedatives. However, it may be noted that long-term use of hypnotics (>4 weeks) is not recommended as per a study in JNCCN (Journal National Comprehensive Cancer Network) by Oxana Palesh et al.[13]

It is necessary to understand that pharmacologic interventions must be complemented by prompt initiation of non-pharmacologic interventions to achieve best outcomes in sleep in gynaecologic cancer patients. Some non-pharmacologic interventions frequently implemented are increase in physical activity, Cognitive Behavioural Therapy (CBT), maintaining good sleep hygiene.

Few studies have demonstrated favourable outcomes of Cognitive Behavioural Therapy (CBT) in sleep in the setting of breast can-

cer. Quesnel et al.[14] conducted a group CBT on breast cancer patients and significant improvements were found in sleep efficiency, total sleep time, mood, and cognitive aspects of quality of life. This study had many parameters like visual inspection of data, Intervention Time Sleep Analysis (ITSA), polysomnography studies, etc. After treatment, 4 of the 8 participants who completed the intervention (50%) obtained a subjective Sleep Efficiency (SE) rating of 85% and greater, an index often used to identify good sleepers. In addition, of the 7 participants who were evaluated at 6-month follow-up, 5 reported a SE rating of 85% or greater (71%).

Savard et al.[15] studied the effects of group CBT for insomnia in breast cancer survivors, and psychologic and immunologic measures. Objective and subjective sleep measures were recorded, as well as hypnotic medication use, psychologic distress, quality of life, and immune measures that included enumeration of blood cell count and cytokine production. Results demonstrated improvements in the subjective sleep data in all sleep variables, including sleep-onset latency, wake time, and sleep efficiency. The improvements were maintained for all variables at the 3-, 6-, and 12-month follow-ups, and continued to improve further regarding total sleep time and the insomnia questionnaire filled out by a significant other. A significant decrease in hypnotic drug use was also reported by the participants after the treatment and started experiencing improvements in psychologic variables like anxiety, depression, global quality of life, and fatigue. The analysis of immunologic measures showed that treated participants had higher cytokine production (ie, IL-1-β, interferon γ) and lower increases of lymphocytes, which then increased at follow-up, as did the leukocyte counts.

Another notable study, by Soetrisno et al.[16] conducted double-blind RCT in which 30 subjects of advanced cervical cancer (IIB-IV) were randomized into two arms based on treatment with psycho-curative intervention consisting of cognitive, spiritual, social, and physical support. The study demonstrated that the average of cortisol in the treatment group is decreased about 5.19 after psycho-curative intervention, as opposed to 1.07 in control. The average of anxiety in the treatment group is decreased about 18.0 after psycho-curative intervention vs. control group decreased into 8.74. The average quality of life in the treatment group is increased after psycho-curative intervention about 7.61, while in control group is constant. These results were statistically significant.

CONCLUSION

Various studies as enlisted have emphasized that the prevalence of sleep disturbance is higher in cancer patients than the general population and that it may lead to mood disturbances, decreased compliance to intervention and declining prognosis in these groups.

Pro-inflammatory cytokines are frequently implicated in chronic sleep disturbance and cancer patients had derangement in cytokine levels. There is immense need for extensive research on medications targeting these cytokines in the setting of gynaecologic malignancies.

The treatment strategy must involve prompt introduction of antiemetics, analgesics, anti-depressants, and mild sedatives. Their introduction as a regular regimen must be considered, especially in a metastatic setting. However, it may be noted that long-term use of hypnotics (>4 weeks) is not recommended due to its adverse effects and clinical trials addressing safety in long term use in gynaecologic malignancies are still underway and warranted.

Non-pharmacological interventions such as CBT for insomnia may be incorporated. Hence the importance of integration of sleep therapists in the oncology care is justified. Patients must also be counselled for physical activity including simple limb stretching exercises and to frequently mobilize themselves. Meditation, yoga, aroma therapy have not been well studied in this setting, but patients may practise in an attempt to increase their quality of life.

RECOMMENDATIONS

As per NCCN (National Comprehensive Cancer Network) guidelines, as an overview, sleep hygiene education, CBT (preferred) and pharmacologic interventions (if safe) are recommended in general for cancer patients with insomnia. Prompt sleep specialist referral is advocated in a setting of circadian rhythm disorder. Patients are encouraged to maintain a sleep log or a diary to effectively study the disruption. Treating the organic causes of sleep disruption must be prioritized.(Table 2 & 3)

Table 2. The following FDA approved drugs[17] may be considered by physicians or oncologists after carefully assessing for safety as an adjunct to Cognitive Behavioural therapy.

Agent	Helps with sleep initiation	Increases total sleep time	For Sleep initiation and maintenance
Zolpidem	+	+	-
Zolpidem CR	+	+	+
Eszopiclone	+	+	+
Zaleplon	+	-	-
Ramelteon	+	+/-	-
Doxepin	-	+	+
Temazepam	+	+	+
Suvorexant	+	+	+

Table 3. Cognitive Behavioural Treatments[18]

Strategy	Goal
Stimulus Control	Associate the bed/bedroom as a place for sleep or sexual activity only
Sleep restriction	Improve sleep continuity by • Limiting time spent in bed • Maintaining a regular sleep schedule by keeping a standard bedtime and wake time every day.
Cognitive therapy	Challenge survivor's maladaptive beliefs and misconceptions about sleep disturbances.
Relaxation training	• Reduce physiologic and cognitive arousal at bedtime • Techniques include progressive muscular relaxation, deep breathing, meditation, yoga and biofeedback.

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