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Sleep Disturbances in Cancer

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One of the major complaints of cancer patients is disturbed sleep.[1,2] Patients with cancer complain of difficulty falling asleep, difficulty staying asleep, and non-restorative sleep, before, during, and for years after treatment.[3] Although some studies have explored the prevalence of sleep disordered breathing (SDB) in head and neck cancer patients,[4,5] and some studies examined limb movements in sleep among breast cancer patients,[6] the majority of sleep studies conducted in cancer patients have almost exclusively examined insomnia.

PREVALENCE OF SLEEP DISTURBANCES

Sleep disturbances in general are reported among 30% to 75% of newly diagnosed or recently treated cancer patients, a rate that is about two times as high as that in the general population.[1,2] Insomnia symptoms in cancer have varied from one study to the other, with rates ranging from 30% to 50%.[3,7] The prevalence of sleep complaints in cancer patients has mostly been examined in cross-sectional studies using convenient samples and heterogeneous definitions and measures of sleep disturbances. Most of the early studies used subjective questionnaires to examine self-reported sleep disturbances, rather than objective measures.

Subjective Sleep Measures

Cancer patients report higher rates of sleep disturbances than the general population. Anderson and colleagues[8] compared 354 cancer patients, 72 psychiatric patients, and 290 non-patient volunteers and found that 62% of the cancer patients reported moderate to severe sleep disturbance, while only 30% of volunteers and 53% of depressed patients reported the same complaint.

Patients with different types of cancer reported different kinds and different rates of sleep problems. In a survey among more than 1,000 patients with different types of cancer and at different treatment phases, 31% reported insomnia, 28% reported excessive sleepiness, and 41% complained of restless legs.[9] Lung cancer patients had the highest or second-highest prevalence of sleep problems in general, while breast cancer patients had a high prevalence of insomnia and fatigue. In another survey, Savard et al[6] studied the prevalence of insomnia in 300 women with breast cancer and found that 19% met the diagnostic criteria for insomnia, with 95% of the cases being chronic insomnia. In addition, they found that in greater than 50% the onset of insomnia preceded the breast cancer diagnosis; however, 58% of the patients reported that cancer aggravated their sleep problems.

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Other prevalence studies relied on telephone surveys. Engstrom et al[10] administered an extensive and sleep-specific telephone survey to 150 patients with lung or breast cancer in various stages of treatment undergoing a variety of treatments. Of those interviewed, 44% reported a sleep problem in the previous month, but only about 17% communicated the problem to their doctors. In the second phase of the survey, another group of cancer patients (n = 20) was interviewed, 45% of which reported a sleep problem in the prior month and half of which rated the sleep problem as moderate, severe, or intolerable. The most frequent type of sleep complaint was awakening during the night, reported by more than 90% of the patients. About 85% complained of sleeping fewer hours than normal, 75% complained of difficulty in getting back to sleep, and 39% reported napping at unusual times such as midmorning and mid-afternoon. These results help identify the type of sleep complaints experienced by cancer patients.

Although much less studied, sleep disturbances have been reported to be very common in patients with advanced cancer. It was reported that 30% of 123 patients with advanced cancers reported sleeping less than 5 hours per night, suggesting significant sleep problems.[11] In a study of 100 palliative care patients attending to a pain and symptom control clinic, 72% reported sleep disturbances, among which 63% reported difficulty staying asleep and 40% reported difficulty falling asleep.[12] In a prospective study, 15.3% of 209 patients with terminally ill cancer self-reported sleep disturbances when they registered to a palliative care unit, a rate that increased to 25.9% at their admission.[13] Another study found that patients with advanced lung cancer reported poorer sleep and more daytime sleepiness than healthy controls and that sleep disturbances of lung cancer patients were characterized by breathing difficulties, cough, nocturia and frequent awakenings, which may be suggestive of SDB.[14]

Another effective way to obtain information about sleep disturbances is by extrapolating information from data on sedative/hypnotic use. In an early study, Derogatis et al[15] found that the most frequent psychotropic prescription in cancer patients was for hypnotics, accounting for 48% of total prescriptions. In addition, out of 814 total prescriptions for hypnotics, “sleep” was the physician’s stated reason for the prescription in 85% of cases compared to 14% for “medical procedure,” 1% for “nausea/vomiting,” 1% for “psychological distress,” none for “pain,” and none for “other.” Ten years later, the results were replicated, that is, 44% of about 400 prescriptions from more than 200 consecutive cancer clinic patients were for hypnotic medications.[16] The patient sample in this particular study encompassed a range of cancer diagnoses and disease severity, and the time since diagnosis varied from 1 to 204 months (mean 23 months). The interpretation of this large number of prescriptions for hypnotics was that sleeping difficulties were a major problem in cancer patients.

Objective Sleep Measures

The gold standard for recording sleep is polysomnography (PSG), ie, overnight sleep measurements that record brain waves, eye movement, muscle tension, and often respiration, heart rate, and leg movements. Although not invasive, PSG recordings can be cumbersome, particularly for cancer patients who are already fatigued or in pain. Therefore, only a few studies have used PSG to study sleep in cancer.

Silberfarb et al1[7] compared lung cancer patients, breast cancer patients, insomnia patients, and normal volunteers with PSG findings and found that, as expected, patients with insomnia had the shortest total sleep time of all the groups. Although the lung cancer patients spent more time in bed, they did not sleep more than the breast cancer patients or than the normal controls. The lung cancer patients, therefore, had lower sleep efficiency (the percent of time in bed actually spent asleep) as well as longer sleep onset latency (time to fall asleep) and spent more time awake during the night than those with breast cancer or the

normal sleepers. Our laboratory collected PSG data immediately after chemotherapy in 33 breast cancer patients and found that patients experienced disturbed sleep with more time spent in lighter levels of sleep (stages 1 and 2) and less time spent in deep (stages 3/4) or REM sleep. These women also spent more time awake with lower sleep efficiency than the general population, even after the completion of their chemotherapy.[18]

A few studies have also used PSG to examine the prevalence of other specific sleep disorders. In the Silberfarb et al[17] study, none of the cancer patients were found to have SDB, but there was a higher preponderance of periodic limb movements in sleep (PLMS) in the cancer patients than in controls or insomnia patients. In our own data, we reported that 36% of breast cancer patients had PLMS.[18] Because PLMS is treatable, these data suggest that it is important to rule out PLMS as a cause of sleep disturbance in patients with cancer.

More recently, an elevated prevalence of obstructive sleep apnea (OSA) has been found in patients with head and neck cancer, although rates were quite varied (from 12% to 91.7%) in the small scale studies (from 17 to 33 patients) that have been published.[4,5] In breast cancer patients, our laboratory found that 48% of the women had at least five respiratory events per hour of sleep,[19] a substantially higher prevalence than that reported in age-comparable women who did not have cancer.

Since PSGs can be difficult to record, many researchers have used actigraphy to study sleep/wake patterns in cancer patients. An actigraph, a small device about the size of a large wrist watch, is worn on the wrist of the non-dominant hand and records movement via motion-sensitive accelerometers. Special algorithms have been developed to estimate sleep and wake time from the movement, and correlation studies with EEG suggest high reliability.

Miaskowski and Lee[20] recorded wrist actigraphy over a 48-hour period in 24 patients at various time points during radiation therapy for bone metastases. As radiation therapy progressed, the subjective sleep complaints increased. Sleep efficiency declined, and frequent urination, rather than pain intensity, was reported to be the main cause of awakening in the night. In a recently reported pilot study, Payne et al[21] reported that, compared with healthy controls, breast cancer patients had significantly shorter total sleep time as estimated from actigraphy.

In the study from our laboratory, actigraphic sleep measures and patient reports of sleep quality were measured in 82 women before and during chemotherapy for breast cancer. Results showed that breast cancer patients were already complaining of sleep problems before the start of chemotherapy,[22] and actigraphic recordings confirmed that the women were asleep on average for only 77% of the night. During treatment, the percentage of sleep dropped to 74%.

RISK FACTORS OF SLEEP DISTURBANCES

General Factors

Most studies on sleep problems in cancer have been conducted in women with breast cancer. The population of women with breast cancer is possibly more prone to insomnia for various reasons, including disruption of sleep due to increased frequency and severity of the hot flashes associated with sudden menopause secondary to the breast cancer treatment. Other possible factors include increased depression and anxiety and fatigue levels following the breast cancer diagnosis.

These risk factors have been confirmed in a few studies. Savard et al[6] studied prevalence, clinical characteristics, and risk factors for insomnia in 300 breast cancer patients and found that factors associated with high risk of insomnia were sick leave, unemployment,

widowhood, lumpectomy, chemotherapy, and a less severe stage of cancer at diagnosis. Lower performance status, anxiety, depression, and confusion were reported to be associated with sleep disturbance in advanced cancer patients. In a survey of 982 different types of cancer patients, Davidson and colleagues[9] found that insomnia-related risk factors included fatigue, age, restless legs, sedative/hypnotic use, low or variable mood, dreams, concerns, and recent cancer surgery. A study of palliative care patients who attended a pain and symptom control clinic, difficulty falling asleep was mostly associated with fatigue and anxiety, while early awakening was more importantly associated with fatigue.[12] In another prospective study in terminally ill patients with cancer, being younger, having diarrhea, and living alone were significantly associated with sleep disturbance. An increase in psychological distress was the only significant predictive factor for the development of sleep disturbances between registration and admission to a palliative care unit.[13]

Radiation and chemotherapy are both reported to produce sleep disturbances. However, as mentioned above, some studies have shown that sleep disturbances already exist before the start of treatment. Cimprich[23] administered self-report items relating to sleep quality, fatigue, and distress to breast cancer patients who had not yet undergone treatment. Insomnia was correlated with high levels of distress and was the most frequent symptom, with 88% of the sample reporting difficulty sleeping. Subjective reports of distress and anxiety were correlated with insomnia, and even before treatment had begun, self-ratings of fatigue and sleep difficulty were high. In patients whose self-ratings of anxiety (as well as anger) were low, levels of insomnia and fatigue were still high. Data from our laboratory showed that disturbed sleep pre-treatment was correlated with fatigue, depressive symptoms, and functional outcome in breast cancer patients.[22] Sleep quality during chemotherapy was associated with the prevalence and severity of pre-treatment symptoms.[24] This contrasts with the general notion that disturbed sleep prior to treatment is attributable to the increased anxiety and stress accompanying the recent diagnosis of a life-threatening illness.

Pain and psychiatric disorders (eg, depression and anxiety) have also been reported as possible causes of poor sleep in cancer, as these factors may work together to induce sleep difficulties. As Engstrom et al[10] stated, pain may be the cause of nocturnal awakenings, but the usual return to sleep is prevented by psychological distress. Lewin and Dahl[25] pointed out that in a variety of medical conditions, the management of pain interrelates with sleep quality in many ways. They theorized that because sleep leads to recovery and repair of tissue and may offer a temporary cessation of the psychological awareness of pain, poor sleep can lead to difficulty in managing pain. In this way, a cycle of pain and poor sleep may become self-perpetuating. However, there are surprisingly few studies supporting the notion that pain leads to disrupted sleep. On the contrary, Silberfarb and colleagues[17] compared 32 cancer patients (15 breast cancer, 17 lung cancer), 32 age- and sex-matched normal volunteers, and 32 patients with insomnia. They found that only breast cancer patients complained of pain prior to bedtime; however, their sleep quality was not significantly affected. The poor sleep quality of the insomnia and lung cancer patients was not associated with reports of pain.

Pain of cancer patients is often treated with opioids. A common side effect of opioids is sedation, yet the relationship between opioids use and sleep has not been well studied. Limited PSG data show that opioids decrease REM sleep and slow-wave sleep,[26] suggesting that rather than improving sleep by being sedated, opioids may contribute to the sleep disturbances in cancer patients with chronic pain. In addition, the most serious adverse effect of opioids is respiratory depression, which may exacerbate the hypoxemia in individuals with SDB and thus lead to more interrupted sleep.

The relationship between sleep disturbances and depressive symptoms are also not well described in cancer patients. It is known that insomnia is often comorbid with depression, that sleep disturbance is a risk factor of depressive symptoms, and that the amount of insomnia in cancer patients has been shown to be as high as the amount of insomnia found in depressed patients. However, studies revealed that depression and sleep disturbances already existed before the start of cancer treatment.[22,23] This suggests that sleep problems may be independent of these psychological/physiological factors.

Biological Rhythms

Although circadian rhythms and sleep have been widely studied in healthy individuals and in patients with other illnesses, little is known about the links between these domains in cancer. Studies among animals and humans suggest that cancer itself may be a result of disturbed biological rhythms. The disruptions in biological rhythmicity are relevant to cancer, to the mitotic properties of cancerous cells themselves, to the treatments of cancer and the time of day of their administration, and possibly to the quality of life in cancer patients. There is growing interest in examining the biological rhythms of cancer patients. Actigraphy is a convenient and effective instrument to measure circadian activity rhythms.

Mormont et al,[27] using actigraphy, studied the circadian rhythm of the rest/activity cycle and of serum cortisol, leukocyte counts, and neutrophil counts in patients with metastatic colorectal cancer for 3 consecutive days prior to beginning chronomodulated chemotherapy. Patients with marked activity rhythms (ie, greater activity when out of bed than when in bed), had a fivefold higher survival at 2-year follow-up than those with less synchronized rhythms. Patients with marked activity rhythms also had better quality of life and reported significantly less fatigue. Circadian rhythms in activity and in white blood cells were jointly prognostic of response. The authors concluded that the rest/activity cycle can be used to determine prognosis for cancer patients' survival and tumor response. Our laboratory also used actigraphy to measure circadian activity rhythms and sleep/wake patterns in breast cancer patients. The circadian rhythms were robust at baseline, but became desynchronized during chemotherapy. This desynchronization was correlated with fatigue, low daytime light exposure, and decreased quality of life.[22,28]

Circadian rhythms can influence tissues and cells as well as sleep/wake activity. Growing evidence from cancer patients indicate that there a strong correlation between sleep disturbances and interrupted circadian rhythms.[1]

Inflammatory Markers

Cytokines are non-antibody polypeptides secreted by inflammatory leukocytes and some nonleukocytic cells and act as intercellular mediators. Inflammation is now recognized as a critical component of tumor progression. Cytokines are not only induced by infectious agents but can also be induced by cancer cells. Elevated levels of cytokines have been found in the blood, ascites, pleural effusions, and urine of patients with cancer. Recent data suggest that elevated cytokines in cancer patients are correlated with circadian parameters.[29] Because cytokines are generally elevated in cancer patients, cytokines may also play a role in the sleep disturbances. Clinical and animal studies suggest that cancer-related symptom clusters, such as sleep disturbances, circadian rhythms patterns, pain, fatigue, cognitive dysfunction, and affective symptoms may share common cytokine-based neuroimmunologic mechanisms.[30,31]

Some inflammatory cytokines, such as interferon (IFN)-alpha, interleukin (IL)-2, and TNF-alpha are used in the treatment of patients with particular cancers. Systemic administration of cytokines often leads to development of a condition known as the systemic inflammatory

response syndrome (SIRS), such as lethargy, weakness, malaise, listlessness, inability to concentrate, fatigue, anorexia, fever, and sleep changes.[30] Kelley et al[32] collectively termed these non-specific changes "sickness behavior." These "sickness behaviors" are a kind of protective reaction of the CNS to the organism itself. Peripherally produced cytokines may affect the central nervous system through transport mechanisms that permit their passage into brain tissue through the blood-brain barrier and by vagus nerve stimulation. They then affect both skin and core body temperature through the release of fever regulating hormone prostaglandin E2 and through stimulating the synthesis and release of corticotropin-releasing factor in the hypothalamus, which then impacts sleep-wake states.[32] Significant correlations have been reported between elevated serum cytokines, serum cortisol rhythm and 24-hour rest-activity rhythm, and tumor-related symptoms in metastatic cancer patients.[29] This suggests a possible role of cytokines mediating an array of signals through the hypothalamic-pituitary-adrenal axis or the circadian axis, which will consequently affect the sleep wake cycle and result in sleep disturbances.

Some cytokines have been reported to be directly correlated to sleep disturbances. Excessive daytime sleepiness is associated with elevated plasma cytokines, and sleep deprivation can cause elevation of proinflammatory cytokine levels. Results of numerous animal and clinical studies indicate that at least two cytokines, IL-1 and TNF, may be classified as sleep regulatory: activation of the IL-1 and/or TNF systems increase NREM sleep and suppress REM sleep and inhibition of these systems decreases spontaneous NREM sleep. Elevated IL-6 may modulate these effects by IL-1 and TNF.[33] Data from our laboratory showed that inflammatory markers such as vascular endothelial growth factor (VEGF) and soluble intercellular adhesion molecule-1 (sICAM-1) were significantly elevated during chemotherapy in breast cancer patients, and the elevated VEGF levels were associated with poorer sleep during treatment.[34]

Sleep disturbances may be a direct result of the cytokines' effect on the brain. Cytokines have been studied widely in cancer patients, but further research is needed. These studies will help to understand the mechanisms of sleep disturbances and other cancer-related symptoms and possibly lead to new treatments for these complaints.[31]

SUMMARY

In summary, the risk factors of sleep disruptions in cancer patients are multifactorial. Savard and Morin[7] summarized insomnia-related factors in cancer into three categories: (1 predisposing factors that increase the individual's general vulnerability to develop insomnia, such as hyper-arousability, being female, aging, and a personal and a familial history of insomnia; 2) precipitating factors that trigger the onset of sleep disturbances, such as the cancer itself, cancer-related emotional impact and functional loss, and cancer-related treatments and symptoms such as pain, and delirium; and 3) perpetuating factors that contribute to the maintenance of sleep disturbance over time, such as maladaptive sleep behaviors and faulty beliefs and attitudes about sleep. Based on the research findings, it is likely that sleep disruptions in cancer patients, particularly insomnia, are more likely comorbid with cancer and with other cancer-related symptoms, rather than secondary to cancer treatments and other cancer-related symptoms, such as fatigue, pain, and depression.

TREATMENT OF SLEEP DISTURBANCES IN CANCER

Pharmacotherapy

Pharmacologic interventions are the most common treatment for sleep disturbances in general population. The National Institutes of Health (NIH) State-of-the-Science Conference on Insomnia[35] concluded that the newer, shorter acting benzodiazepine receptor agonists are

efficacious in the management of insomnia. The conference also concluded that the frequency and severity of adverse effects associated with these agents are much lower than those seen with the older, longer acting benzodiazepines. It has also been concluded that all antidepressants, antihistamines (H1 receptor antagonists), and antipsychotics have potentially significant adverse effects, thereby raising concerns about the risk-benefit ratio and thus their use in the treatment of chronic insomnia cannot be recommended.

Although pharmacotherapy is the most prescribed therapy for cancer patients with sleep disturbances,[7,9] there is a paucity of studies related to pharmacologic interventions in cancer patients. A recent review[2] concluded that evidence is not sufficient to recommend specific pharmacologic interventions for sleep disturbances in cancer patients. Clinicians need to evaluate the relative effectiveness and side-effect profiles of pharmacologic agents, and researchers need to be challenged to evaluate the impact of pharmacologic treatment on sleep disturbances among cancer patients.[2]

Cognitive Behavioral Therapy

Many nonpharmacologic interventions, such as cognitive and behavioral therapies, have been developed and tested in otherwise healthy people with sleep disturbances. Numerous randomized controlled clinical trials in insomnia among general populations have shown that cognitive behavioral therapy (CBT) is at least as effective and maybe more effective than pharmacological treatment for insomnia. The NIH State-of-the-Science Conference on Insomnia concluded that CBT is as effective as prescription medications for brief treatment of chronic insomnia. The conference also concluded that there are indications that the beneficial effects of CBT, in contrast with those produced by medications, may last well beyond termination of treatment.[35]

Available data suggest that nonpharmacologic interventions are very effective for the treatment of insomnia in cancer. Savard et al[36] conducted a randomized wait-list controlled study on the effects of CBT on insomnia in women with breast cancer. Results suggested that CBT was effective in decreasing sleep complaints as well as decreasing levels of depression and anxiety and increasing quality of life. Therapeutic effects were maintained at follow-up. Fiorentino et al[37] performed a randomized controlled crossover study using CBT among breast cancer survivors with insomnia and found that CBT improved sleep measured with both subjective (sleep diary and questionnaire) an objective (actigraphy) measurements.

Bright light therapy is another nonpharmacological treatment option that appears promising. Preliminary data from our laboratory suggest that increased bright light exposure may improve sleep (increased total sleep time, decreased wake time during the night, and decreased daytime napping) and fatigue during chemotherapy for patients with breast cancer.[38,39]

Combination of Therapies

The combination of pharmacologic and nonpharmacologic therapies has been studied in non-cancer populations, with better short-term improvement found with the combination than with each therapy alone. However, the behavioral therapy alone produced better long-term gains. CBT strategies can easily and effectively be integrated into the cancer care routine.[7] As reviewed by Theobald, treating insomnia in cancer patients with a combination of pharmacologic and nonpharmacologic therapy may have a positive impact not only on the insomnia itself but also on related symptoms, including pain, fatigue, and psychological distress.[40]

CONCLUSION AND FUTURE DIRECTIONS

Sleep disturbances in cancer patients are common and multifactorial. Sleep disturbances, particularly insomnia, are likely comorbid with cancer. In addition, the cancer itself, cancer-related symptoms, and cancer treatment may all exacerbate sleep problems. More studies are needed to determine baseline levels of sleep and sleep disturbances in cancer patients in order to address this question. The sleep disturbances may share common cytokine-based neuroimmunologic mechanisms with other symptoms, such as pain, fatigue, depression, disturbed circadian rhythms, and cognitive dysfunction. Further animal and clinical trials are needed to help understand the cellular and molecular mechanisms of those symptoms, particularly the roles of cytokines, and to help develop biological interventions.

Pharmacologic treatments are still the most common interventions for sleep disturbances in cancer patients, yet combined CBT and pharmacotherapy may be more advantageous due to the rapid effect of pharmacological therapy and durability of cognitive behavior modification. Nonpharmacologic treatments and combined therapeutic methods need to be developed and further tested in cancer patients. The long-term goal of research on sleep disturbances in cancer patients should be to illuminate approaches that might improve the quality of life during treatment and/or the course of treatment itself.

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