

# Cancer Pain, Fatigue, Distress, and Insomnia in Cancer Patients

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Insomnia is common among cancer patients, occurring in ~30% to 50% of the cancer population. The interactions between cancer pain, insomnia, fatigue, and depression/anxiety are complex, warranting treatment plans that focus not only on the relief of specific symptoms to improve quality of life but also on the impact of treatment on other related symptoms. Pain is one of the most common symptoms experienced by cancer patients and is one of the primary factors that precipitate insomnia in this population. Fatigue is also commonly reported by cancer patients, with a prevalence of nearly 80% in some tumor types. Cancer-related fatigue occurs most often after surgery, chemotherapy, radiotherapy, or immunotherapy and has been reported by cancer patients to be the major obstacle to normal functioning and a good quality of life. Insomnia in cancer patients often occurs in association with psychological disorders such as depression or anxiety. Sleep disturbances are associated with aberrant patterns of cortisol secretion, such as those found in insomnia, which are known to significantly depress the immune system, particularly the cells of the immune system responsible for mounting a defense against tumors. Evidence suggests that management of insomnia through a combination of pharmacologic and nonpharmacologic means can have a positive impact not only on insomnia but also on related symptoms and, consequently, on overall health and quality of life. Although the treatment of insomnia in cancer patients can improve cancer-related fatigue, immune functioning, and overall quality of life, insomnia in the context of cancer is still undertreated. Physicians should use hypnotic agents appropriately and be aware of the reduced potential for producing tolerance and dependence with the nonbenzodiazepine hypnotic agents. The management of insomnia in cancer patients should include a global treatment plan designed to address not only the underlying sleep disturbance but also the related symptoms that may contribute to insomnia or occur as a result of it. (*Clinical Cornerstone*. 2004;6[Suppl 1D]:S15–S21) Copyright © 2004 Excerpta Medica.

Insomnia is one of the most common symptoms among cancer patients, occurring in ~30% to 50% of the cancer population.<sup>1</sup> Insomnia in cancer patients is often part of a cluster of interrelated symptoms, including pain, fatigue, anxiety, and depression. In a study designed to validate a cancer symptom assessment instrument, a cluster of symptoms was highly prevalent across tumor types: 40% to 80% of patients experienced lack of energy, pain, drowsiness, dry mouth, insomnia, or symptoms indicative of psychological distress.<sup>2</sup> Each of these symptoms can contribute to the maintenance of the others, resulting in a significant adverse impact on quality of life. For example, untreated

ed cancer pain can lead to depression or anxiety, which in turn can cause insomnia. At the same time, medications to treat cancer pain or to relieve the side effects of analgesics can cause insomnia. Insomnia is also known to be a significant predictor of severe fatigue in cancer patients and plays a role in the maintenance of cancer-related fatigue.<sup>3,4</sup> Cancer-related fatigue can lead to behaviors (eg, daytime napping) that then result in nighttime sleep difficulties. Sleep disturbances can also lead to aberrations in cytokine and stress hormone levels, which can suppress immune function and lead to decrements in overall health.<sup>5,6</sup> Thus, the interactions between cancer pain,

insomnia, fatigue, and depression/anxiety are complex, warranting treatment plans that focus not only on the relief of specific symptoms to improve quality of life, but also on the impact of treatment on other related symptoms.

### KEY POINT

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### INSOMNIA AND CANCER PAIN

Pain is one of the most common symptoms experienced by cancer patients<sup>7</sup> and is one of the primary factors that precipitate insomnia in this population.<sup>1</sup> Approximately 25% of newly diagnosed patients, 33% of patients undergoing treatment, and 75% of advanced-cancer patients experience pain.<sup>7</sup> In a sample of patients with lung and colon cancer who were experiencing pain, more than half (56%) reported sleep disturbances due to pain.<sup>1</sup> In a larger study of 1635 cancer patients referred to a pain clinic, 59% of patients experienced insomnia in addition to pain.<sup>8</sup> Moreover, those with more severe pain reported more sleep disturbances. There is also evidence that sleep disturbances may increase one's sensitivity to pain.<sup>9</sup>

Insomnia related to cancer pain may be due to the pain itself or to the medications used to treat the pain. Untreated pain may prevent cancer patients from falling asleep or may lead to nocturnal awakenings, making it difficult for patients to maintain sleep. However, treatment of the pain with opioid analgesics, for example, can cause a range of side effects, including nausea, somnolence, dizziness, constipation, and headache. Somnolence, particularly during the daytime, can interfere with nighttime sleep. The use of adjuvant medications to relieve the side effects of opioids can also exacerbate insomnia. For example, antiemetic agents such as prochlorperazine, metoclopramide, and granisetron are recommended for the management of opioid-related nausea and vomiting<sup>7</sup>; however, these agents are known to cause

insomnia.<sup>1</sup> Similarly, psychostimulant drugs such as methylphenidate may be used to relieve opioid-induced sedation, but these drugs may in turn cause symptoms of anxiety and insomnia.<sup>7,10</sup> Even cognitive-behavioral therapy (CBT) for the treatment of pain may contribute to the maintenance of insomnia symptoms.<sup>9</sup> Cancer patients experiencing refractory pain may be referred to specialized pain clinics or pain management teams. However, these specialists tend to use anesthetic agents or sedatives for pain control, with less emphasis on improving sleep in the long run. Sedatives can cause daytime somnolence, which, as discussed, can lead to nighttime sleep difficulties. Therefore, in cancer patients with insomnia due to pain, the management of pain alone—whether through pharmacologic or nonpharmacologic means—may not produce corresponding improvements in insomnia. The complex relationship between pain, pain medications, and insomnia may also help explain how insomnia can become chronic in many patients with cancer.

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### INSOMNIA AND CANCER-RELATED FATIGUE

Fatigue is the most common symptom reported by cancer patients,<sup>3</sup> with a prevalence of nearly 80% in some tumor types.<sup>2</sup> Cancer-related fatigue occurs most often after surgery, chemotherapy, radiotherapy, or immunotherapy and has been reported by cancer patients to be the major obstacle to normal functioning and a good quality of life.<sup>10</sup>

Sleep disturbances are often associated with fatigue. The relationship between insomnia and fatigue is complex. It may be that difficulties sleeping at night lead to daytime fatigue, which in turn leads to behaviors (eg, daytime napping) that help perpetuate insomnia. Conversely, fatigue resulting from anemia or other physiologic effects of cancer and/or its

treatment may lead directly to daytime sedation and, consequently, difficulties sleeping at night. Anderson et al,<sup>3</sup> in a study comparing fatigue in cancer patients, depressed patients, and community-dwelling adults, found that sleep disturbances were a significant predictor of fatigue in cancer patients. Moreover, cancer patients who reported sleep disturbances were significantly more likely to report high levels of fatigue than patients with no sleep disturbances. Interestingly, in this study, sleep disturbance was not a significant predictor of fatigue among patients with depression. This suggests that the nature of fatigue associated with cancer is different from that associated with depression or other illnesses.<sup>3</sup> It further suggests that treatment of depression in cancer patients—with antidepressants, for example—may not necessarily relieve cancer-related fatigue or associated sleep disturbances.

### KEY POINT

**The complex relationship between pain, pain medications, and insomnia may also help explain how insomnia can become chronic in many patients with cancer.**

The National Comprehensive Cancer Network (NCCN) has identified 7 factors that can contribute to fatigue in cancer patients: pain, emotional distress, sleep disturbance, anemia, nutrition, activity level, and other comorbidities.<sup>7</sup> Accordingly, NCCN treatment recommendations state that the first step in fatigue management should be to treat any of these identifiable contributing factors. Sleep disturbances, if identified, should be managed with sleep hygiene techniques with or without the addition of an hypnotic agent.<sup>7</sup> Sleep hygiene and other nonpharmacologic approaches such as exercise, stress reduction, and relaxation therapy have been used successfully to relieve cancer-related fatigue.<sup>7</sup>

Although fatigue and insomnia are closely related, the treatment of fatigue in cancer patients may not produce corresponding improvements in insomnia. Several classes of drugs are used in the treatment of

cancer-related fatigue, including psychostimulants, antidepressants, and corticosteroids. When other causes of fatigue have been ruled out, psychostimulants such as methylphenidate are recommended when pharmacologic treatment is deemed appropriate.<sup>7</sup> Methylphenidate has been studied more extensively in the cancer population than other drugs in this class and is often the first drug administered to relieve cancer-related fatigue.<sup>10</sup> However, the use of psychostimulants is associated with adverse effects such as anorexia, tremor, anxiety, delirium, tachycardia, and, most importantly, insomnia.<sup>10</sup> These adverse effects may contribute to the maintenance of insomnia symptoms and in turn complicate the treatment of cancer-related fatigue. Antidepressants, including the selective serotonin reuptake inhibitors, tricyclic secondary amines (eg, nortriptyline and desipramine), and bupropion, have been tried both in depressed and non-depressed patients with cancer-related fatigue, but the data and clinical experience with these agents for this indication are limited.<sup>10</sup> Corticosteroids (eg, dexamethasone, prednisone) in low doses are sometimes recommended to relieve fatigue in patients with advanced cancer.<sup>7,10</sup> However, dexamethasone and corticosteroids in general are highly likely to cause insomnia. In fact, insomnia is one of the most common side effects of short-term steroid use.<sup>11</sup> Thus, the treatment of fatigue may not lead to relief of fatigue-related insomnia; in fact, the medications used can often contribute to the maintenance or worsening of the insomnia symptoms.

### INSOMNIA AND PSYCHOLOGICAL DISTRESS

Insomnia in cancer patients often occurs in association with psychological disorders such as depression or anxiety. Although reported prevalence rates vary, it has been estimated that ~50% of all cancer patients have anxiety and/or depressive disorders.<sup>1</sup> Insomnia is often a symptom of depressive and anxiety disorders, but the high prevalence of insomnia in cancer patients cannot be explained entirely by the higher prevalence of mood disorders in this population. In many cases, insomnia, especially persistent or chronic insomnia, may lead to mood disorders or may exacerbate them. Patients with insomnia may feel helpless and unable to cope with their cancer, leading to symptoms of depression or anxiety. Studies have shown

that patients with persistent insomnia are at greater risk for developing psychological disorders such as depression and anxiety.<sup>1</sup> Most important, however, is the finding that the risk of developing a depressive disorder is lower when insomnia has been resolved,<sup>12</sup> suggesting that insomnia is a significant risk factor for psychiatric disorders.

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Even in the absence of a diagnosis of clinical depression or anxiety, cancer patients may experience severe physical and emotional distress as a result of the psychological stressors inherent to a diagnosis of cancer and its treatment. Among cancer patients, insomnia is often attributed to thoughts and concerns about cancer and its treatment. In a cross-sectional survey study of insomnia in cancer patients,<sup>4</sup> insomnia symptoms were more often attributed to thoughts and concerns about health, family and friends, the cancer diagnosis, and finances than to the actual physical effects of cancer. The relationship between psychological stress and insomnia is similar to that between pain and insomnia. Sleep disturbances may increase cancer-related anxiety and distress, which then lead to further sleep problems, contributing to a vicious cycle in which insomnia leads to stress and stress leads to insomnia.<sup>13</sup> Indeed, anxiety and stress are known to disrupt the diurnal pattern of stress hormones such as cortisol,<sup>13</sup> and this dysregulation of diurnal cortisol rhythm is associated with sleep disturbances.

### INSOMNIA AND THE IMMUNE SYSTEM

Sleep is vital to human well-being and survival. It follows then that inadequate sleep can cause substantial aberrations in normal functioning.<sup>5</sup> Sleep serves a restorative function, and lack of nonrapid eye movement sleep can have an adverse effect on overall health.

Sleep disturbance, particularly insomnia, is a predictor of cardiovascular and noncardiovascular mortality.<sup>7</sup> Sleep loss is associated with aberrations in the expression of cytokines and a decrease in immune function.<sup>5,6</sup> Insomnia is associated with an increase in norepinephrine levels and decreased activity of natural killer (NK) cells,<sup>6</sup> cells that are important in the antitumor immune response. This suggests that sleep influences the body's ability to fight infection and disease. Insomnia has been reported to be associated with abnormal cortisol secretion patterns, with consistently elevated cortisol levels during the day instead of the normal peak at awakening and gradual decrease during the day.<sup>5</sup> Sephton et al<sup>14</sup> have demonstrated that such abnormal cortisol patterns are associated with reduced NK cell count and activity as well as higher mortality in patients with metastatic breast cancer. Thus, insomnia and the associated potential of decreases in immune function may affect tumor progression in some cancer patients, which in turn has an impact on prognosis and mortality.

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### INSOMNIA AND QUALITY OF LIFE IN CANCER PATIENTS

Insomnia also has a profound impact on daily functioning and quality of life. In a survey of >1000 patients with various types of cancer,<sup>4</sup> the vast majority of those with insomnia reported that their sleep difficulties affected how they felt physically and emotionally as well as their ability to deal with stress, carry out activities of daily living, and concentrate. Fortner et al<sup>15</sup> examined the impact of sleep disturbances on quality of life in patients with breast cancer and found that patients who had sleep disturbances had decreased ability to function in general, greater bodily pain, less energy in daily life, and more mental health problems than patients without sleep diffi-

culties. Patients with sleep difficulties also reported worse emotional health and greater limitations in performing daily tasks due to emotional problems than those without such difficulties.<sup>15</sup> Insomnia, therefore, affects both physical and emotional aspects of quality of life. This suggests that management of insomnia may have a beneficial impact on quality of life.

### **BENEFITS OF INSOMNIA MANAGEMENT IN CANCER PATIENTS**

Insomnia in cancer patients almost always occurs in association with other symptoms, including pain, fatigue, and psychological distress. Although the cause-and-effect relationship is not always clear between these symptoms, there is ample evidence to suggest that management of insomnia through a combination of pharmacologic and nonpharmacologic means can have a positive impact not only on insomnia but also on related symptoms in this cluster and, consequently, on overall health and quality of life.

As discussed, pain management alone may not be sufficient to relieve insomnia symptoms due to cancer pain. Insomnia may still persist after cancer pain has been adequately managed because the analgesic agents as well as the medications used to relieve the side effects of the analgesics may contribute to the maintenance of insomnia symptoms. The use of appropriate hypnotic agents and/or CBT can help relieve insomnia symptoms, whether they are due to cancer pain itself or the medications used to manage cancer-related pain.

Cancer-related fatigue and insomnia follow each other in a difficult cycle. Fatigue due to cancer or cancer treatment (eg, chemotherapy, radiation, immunotherapy) often leads to insomnia, and insomnia in turn contributes to the maintenance of daytime fatigue. Medications designed to relieve fatigue, including psychostimulants, antidepressants, and corticosteroids, may themselves cause anxiety, tremor, and insomnia. A treatment plan for insomnia in cancer patients must therefore take into account the possible effects of therapy on fatigue. For example, treatment of insomnia with long-acting benzodiazepines may produce daytime drowsiness or light-headedness, which may exacerbate cancer-related fatigue.<sup>1,16</sup> The nonbenzodiazepine hypnotic agents (eg, zaleplon, zolpidem) are thought to have more selectivity than the traditional benzodiazepines and fewer residual side effects the

next day.<sup>1</sup> In clinical studies, zaleplon and zolpidem have not been found to be associated with alterations in sleep cycle architecture or clinically significant rebound insomnia.<sup>17</sup> Therefore, the use of nonbenzodiazepine hypnotics along with medications to combat fatigue may help break the daytime fatigue–insomnia cycle.

### **KEY POINT**

**The use of nonbenzodiazepine hypnotics along with medications to combat fatigue may help break the daytime fatigue–insomnia cycle.**

Insomnia that occurs in association with disorders such as clinical depression or anxiety in cancer patients may be relieved by treating the underlying psychiatric disturbance with antidepressants that have sedating properties (eg, trazodone, amitriptyline, doxepin).<sup>1</sup> Use of activating antidepressants (eg, selective serotonin reuptake inhibitors such as fluoxetine) may exacerbate insomnia so that patients treated with these agents may require specific hypnotic agents to address insomnia symptoms.<sup>1</sup> There is insufficient data to support the use of antidepressants such as trazodone to treat insomnia in patients without depressive disorders.<sup>18</sup> As discussed, insomnia, especially persistent or chronic insomnia, is a significant risk factor for psychiatric disorders. Therefore, the treatment of insomnia may help relieve mood disturbances and prevent progression to more serious psychiatric disorders.

Loss of sleep has a direct effect on the diurnal variation of stress hormones and on the immune system.<sup>5,6</sup> Sleep disturbances are associated with aberrant patterns of cortisol secretion.<sup>5</sup> Abnormal patterns of cortisol secretion, such as those found in insomnia, are known to significantly depress the immune system, particularly the cells of the immune system responsible for mounting a defense against tumors.<sup>13</sup> In fact, advanced breast cancer patients with these types of aberrant cortisol patterns had much lower NK cell counts and activity and had a much higher mortality rate than those with normal patterns of cortisol activity.<sup>14</sup> From these data, it

may be inferred that treatment of insomnia in cancer patients through the use of hypnotics can help normalize cortisol patterns and perhaps restore immune system activity.

### **ISSUES IN THE TREATMENT OF INSOMNIA IN CANCER PATIENTS**

Although the treatment of insomnia in cancer patients may improve cancer-related fatigue, immune functioning, and overall quality of life, insomnia in the context of cancer is still undertreated. Treatment of insomnia in cancer patients may be complicated by several issues. Patients may be reluctant to report insomnia symptoms, dismissing them as unimportant relative to the cancer.<sup>19</sup> Physicians may underprescribe hypnotics because of fear of dependence, side effects, and drug interactions, and may also be reluctant to prescribe additional medications in cancer patients, since these patients are often already receiving multiple drugs as part of therapy or to relieve side effects of therapy.<sup>19</sup> However, both physicians and patients need to be aware of the restorative function of sleep, the importance of sleep for proper immune functioning, and the overall benefits of sleep improvement. Physicians should use hypnotic treatment options appropriately and be aware of the favorable side-effect profiles of the nonbenzodiazepine hypnotic agents and their reduced potential for producing tolerance and dependence. The potential for tolerance and dependence, while a concern in the treatment of chronic insomnia in the general population, may not be relevant in the context of cancer. A useful analogy in this discussion is the use of opioid analgesics to treat cancer-related pain. Opioid analgesics have the potential to cause tolerance and dependence; however, these agents are highly effective in relieving cancer-related pain and improving the quality of life for cancer patients and are therefore considered the first line of treatment for moderate to severe cancer pain. The potential for opioids to cause tolerance and dependence can be reduced by adjusting doses and administering doses around the clock instead of as needed.<sup>17,18</sup> Similarly, the potential for hypnotic agents to cause tolerance and dependence can be reduced by using nonbenzodiazepine agents, using them as needed instead of nightly, and adjusting dose regimens during periods of expected insomnia (eg, using hypnotic agents nightly when insomnia-inducing therapies are used).<sup>17,18</sup>

An understanding of the underlying factors that might be contributing to the insomnia can help formulate an appropriate treatment plan. For example, if insomnia is temporarily related to chemotherapy or use of corticosteroids, hypnotic agents may be prescribed for the duration of therapy. Insomnia that is due to cancer-related pain may be managed by appropriate use of analgesics to manage the pain and hypnotic agents to manage the insomnia associated with pain as well as symptoms that might result from opioid analgesics or medications used to manage the side effects of the opioid analgesics. Insomnia due to depressive disorders may be managed using sedating antidepressants or a combination of activating antidepressants and specific hypnotic agents. Insomnia due to cancer-related fatigue may be managed through a combination of hypnotic agents and CBT designed to break the vicious cycle of fatigue and insomnia.

### **KEY POINT**

**Insomnia due to cancer-related fatigue may be managed through a combination of hypnotic agents and cognitive-behavioral therapy designed to break the vicious cycle of fatigue and insomnia.**

### **CONCLUSIONS**

Insomnia in the context of cancer seldom occurs by itself and more commonly clusters with other related symptoms such as fatigue, pain, and/or emotional distress, all of which can contribute to decreased quality of life. Treatment of these other symptoms may or may not resolve the insomnia and in some cases may contribute to the maintenance of insomnia symptoms. Therefore, the management of insomnia in cancer patients should include a global treatment plan designed to address not only the underlying sleep disturbance but also the related symptoms that may contribute to insomnia or occur as a result of it. A treatment plan that takes into account the effects of therapies on all the symptoms of this cluster can help relieve each symptom, without exacerbating the others. Treatment of insomnia and its associated symptoms

may lead to improved immune functioning and better quality of life for cancer patients.

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