CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will ask their cancer patients about insomnia

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Sleep disturbances in cancer patients: Underrecognized and undertreated

ABSTRACT

Sleep-related complaints are extremely common in patients with cancer but often are not recognized, and even if they are, they are seldom treated. Recognizing insomnia in cancer patients is imperative, as appropriate treatment can improve quality of life.

KEY POINTS

Sleep disturbances, primarily insomnia, profoundly affect all aspects of quality of life.

Insomnia can be caused or worsened by a number of other conditions, such as pain, fatigue, depression, and anxiety, and these in turn can be worsened by insomnia.

Cognitive-behavioral therapy is the treatment of choice for chronic insomnia. Underlying problems should be addressed.

Drugs are often prescribed to help cancer patients sleep but should be used with caution, as there is limited information from clinical trials in this population.

MANY CANCER PATIENTS don't sleep well, for a variety of reasons. It is an important problem: not only does poor sleep worsen quality of life, it may affect prognosis. Moreover, treatment is available.

Yet many physicians caring for cancer patients do not ask about sleep problems, underestimating their impact or focusing on more urgent problems. Also, patients may not want to bring up the topic because they consider poor sleep to be unavoidable and untreatable and because they fear that reporting it may shift the focus of their treatment from trying to cure the cancer to easing its symptoms.

This practical review will help health care professionals avoid the common barriers to diagnosis and treatment of poor sleep in cancer patients. Because there are few data on other sleep disorders such as sleep apnea and restless leg syndrome, we will focus on the most common one in cancer patients—insomnia—and its effects on other symptoms and quality of life.

MORE PATIENTS SURVIVE CANCER NOW

Today, more patients are surviving cancer, but cancer symptoms and the side effects of surgery, chemotherapy, and radiation therapy may persist for years.[1,2] The most common complaints include cancer-related fatigue, leg restlessness, anxiety, insomnia, and excessive sleepiness.[3]

Sleep disturbances appear to contribute to the other problems and are relatively easier to quantify. Most studies of sleep disorders in cancer patients have looked specifically at insomnia,[4] although a few have explored the prevalence of other sleep disorders, such as sleep-disordered breathing and limb movements during sleep.[5]

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The *International Classification of Sleep Disorders*, 2nd edition,[6] defines insomnia as difficulty going to sleep or staying asleep (the latter defined as waking up in the middle of the night, with wakeful episodes lasting more than 30 minutes), early-morning awakenings (waking 30 minutes or more before the intended time), or nonrestorative sleep, causing significant distress or impairment of daytime functioning.

INSOMNIA WORSENS QUALITY OF LIFE

Insomnia significantly worsens quality of life in cancer patients, and if it can be detected and effectively treated, quality of life is likely to improve. Studies in cancer patients have found that those with insomnia:

- Were less able to cope with stress and carry on their activities of daily living[3]
- Were much less able to function and reported more pain, less energy, and greater difficulty in dealing with emotional problems[7]
- Had poor quality of life, both physically and emotionally.[3,8]

PERHAPS MORE THAN HALF OF CANCER PATIENTS HAVE INSOMNIA

Depending on the methods used and populations studied, at least 30% and perhaps more than half of patients with cancer have insomnia (**TABLE 1**).[3,4,8–14] It is one of the most commonly reported complaints in this group,[15–17] and it occurs before, during, and after treatment of cancer.

Although the prevalence may differ in various cancers, it is still higher than in the general population. In a study of about 450 patients with cancer or depression and 300 healthy volunteers, 62% of the cancer patients reported moderate to severe sleep disturbance, compared with 52% of the depressed patients and 30% of the healthy volunteers.[18]

When Davidson et al[3] surveyed nearly 1,000 cancer patients, one-third said they had insomnia. The problem was most prevalent in lung and breast cancer patients.

In a longitudinal study by Savard et al,[13] the prevalence of insomnia declined over time but remained high even at the end of 18 months. It was more prevalent in patients with gynecologic and breast cancer than in those with prostate cancer.[13,19]

Drugs mentioned in this article

Amitriptyline (Elavil)
Chlorpromazine (Thorazine)
Clonazepam (Klonopin)
Diphenhydramine (Benadryl)
Doxepin (Silenor)
Eszopiclone (Lunesta)
Flurazepam (Dalmane)
Hydroxyzine (Vistaril)
Lorazepam (Ativan)
Methylphenidate (Ritalin)
Mirtazapine (Remeron)
Modafinil (Provigil)
Nortriptyline (Pamelor)
Olanzapine (Zyprexa)
Paroxetine (Paxil)
Ramelteon (Rozerem)
Risperidone (Risperdal)
Temazepam (Restoril)
Thioridazine (Mellaril)
Trazodone (Desyrel)
Zaleplon (Sonata)
Zolpidem (Ambien)

SLEEP PROBLEMS ARE UNDERREPORTED

Sleep problems in cancer patients often go unrecognized because patients do not report them. In a survey of 150 patients,[20] 44% reported having had sleep problems during the preceding month. However, only one-third of those with sleep problems told their health care providers. This highlights the need for physicians to address sleep complaints in cancer patients at every visit and, if needed, to refer them to a sleep specialist for further evaluation and management.

Too often, pain is inadequately controlled

INSOMNIA IS OFTEN ASSOCIATED WITH OTHER PROBLEMS

Many things can interfere with sleep in cancer patients: the cancer itself (eg, pain due to tumor invasion), medical treatments (eg, narcotics, chemotherapy, neuroleptics, sympathomimetics, steroids, sedative hypnotics), psychosocial disturbances (eg, depression, anxiety, stress), and comorbid medical issues.

In this population, insomnia is often part of a cluster of symptoms that includes pain, fatigue, depression, and anxiety. These act synergistically, worsening quality of life.[21–24]

Cancer-related fatigue and insomnia

Cancer-related fatigue is a distressing, persistent, subjective sense of tiredness or ex-

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TABLE 1

Selected studies of prevalence of sleep disturbances in cancer patients

Study	No. of patients	Type of study	Time of assessment	Cancer type	Assessment method	Findings
Davidson, 2002[3]	982	Cross-sectional survey	Routine outpatient office visits	Breast, gastrointestinal, genitourinary, gynecologic, lung, and nonmelanoma skin cancers	42-item "Sleep Survey" questionnaire	30% reported insomnia; 22% used tranquilizers
Ancoli-Israel, 2006[10]	85	Actigraphy and cross-sectional survey	Before beginning chemotherapy	Stage I–IIIA breast cancer	72-hour actigraphy, PSQI, MFSI-SF, FOSQ, FACT-B, CES-D	Women reported disturbed sleep, with a mean total PSQI score of 7.0
Miaskowski, 2011[11]	185	Actigraphy and cross-sectional survey	Before beginning radiation therapy	Breast, prostate, lung, brain	48-hour actigraphy, PSQI, GSDS	More than 56% had a global PSQI score > 5 26% had GSDS above the proposed cutoff of > 8 for oncology patients
Liu, 2012[12]	97	Prospective study	Patients undergoing chemotherapy	Newly diagnosed stage I-III breast cancer	Ambulatory actigraphy, PSQI, MFSI-SF	At baseline, 61% of the women reported a PSQI > 5; at the end of treatment, 76% reported a PSQI > 5, and 42% reported a PSQI > 8
Chen, 2008[8]	115	Cross-sectional survey	Patients undergoing chemotherapy	Lung	PSQI, EORTC questionnaire	Patients' mean PSQI score for days with chemotherapy was 6.86 ± 3.83; for days without chemotherapy, the score was 6.23 ± 3.47
Savard, 2011[13]	962	Prospective longitudinal study	From preoperative visit to 18 months after the surgery	Mixed	Insomnia interview schedule	59% had insomnia at baseline; the prevalence of insomnia generally declined over time but remained pervasive even after 18 months (36%)
Sela, 2005[14]	100	Cross-sectional survey	Palliative cancer patients attending a pain and symptom control clinic	Mixed	9-item sleep questionnaire and ESAS	19% reported insomnia before their cancer diagnosis; after diagnosis, 72% did

PSQI = Pittsburgh Sleep Quality Index (interpretation: score ≤ 5 associated with good sleep quality, and score > 5 associated with poor sleep quality); MFSI-SF = Multidimensional Fatigue Symptom Inventory–Short Form; FOSQ = Functional Outcome of Sleep Questionnaire; FACT-B = Functional Assessment of Cancer Therapy–Breast; CES-D = Center for Epidemiological Studies–Depression scale; GSDS = General Sleep Disturbance Scale; EORTC = European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30); ESAS = Edmonton Symptom Assessment System

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haustion that is related to cancer or cancer treatment, that is not proportional to recent activity and that interferes with usual functioning.[25] It has been reported by up to 90% of cancer patients in some studies.[26–28]

Cancer-related fatigue worsens quality of life and is one of the most distressing and persistent symptoms experienced before, during, and after cancer treatment.[29,30] Furthermore, it can lead to sleep disturbances and daytime somnolence and further aggravate insomnia.[31,32] The two conditions are often reported as part of a cluster of interrelated symptoms that include pain, depression, and loss of concentration and other cognitive functions, suggesting that they may share a common etiology.[33–35]

Åhsberg et al[36] examined different aspects of perceived cancer-related fatigue in patients undergoing radiotherapy and found correlations between lack of energy, sleepiness, and cancer-related fatigue.

Current understanding of the possible link between cancer-related fatigue and insomnia suggests that interventions targeting the insomnia and daytime sleepiness could decrease the fatigue as well.[31]

Pain and insomnia in cancer patients

Pain is reported by 60% to 90% of patients with advanced cancer,[37,38] its intensity usually varying with the extent of disease. Too often, it is inadequately controlled.[39] Furthermore, it is thought to contribute to insomnia.[40]

In a study of more than 1,600 cancer patients, nearly 60% reported insomnia in addition to pain.[41] The severity of pain directly correlated with the probability of insomnia.

Conversely, research suggests that sleep disturbances, primarily insomnia, can increase cancer patients' sensitivity to pain.[42] One hypothesis is that adequate sleep is needed to promote processes relevant to recovery from pain, both physiologic (ie, tissue repair) and psychological (ie, transient cessation of the perception of pain signals).[43]

Paradoxically, opioids can worsen insomnia

Cancer pain is often treated with opioids, which, paradoxically, can cause or worsen insomnia.

Although opioids induce sleep, they also depress respiration, and at night, they can cause or worsen sleep-disordered breathing (obstructive or central sleep apnea or ataxic breathing), leading to episodes of hypoxia, arousals, and fragmented sleep.[44] Moreover, opioids can lead to daytime sedation. Further, psychostimulants such as methylphenidate, given to counteract opioid-induced sedation, can cause anxiety and insomnia. Thus, the interaction between cancer-related pain, insomnia, and pain management leads to a vicious cycle. Understanding this process, we can try to break the cycle and help patients with cancer sleep better.

However, how best to treat sleep-disordered breathing in patients taking opioids long-term is not well established.

In general, the primary intervention is to reduce the opioid dose. Practitioners should continually assess the need for these drugs and consider referral to a drug-behavior treatment center to help with discontinuation of opioid use when deemed medically appropriate.[45] Other strategies include positive airway pressure ventilation including continuous positive airway pressure, bilevel pressure devices with backup rate, or adaptive servoventilators. In some cases oxygen supplementation may be required.

Sleep-disordered breathing, when recognized and diagnosed, should be managed in partnership with a sleep specialist.

Cancer patients who can't sleep are more sensitive to pain

Depression and insomnia in cancer patients

By some estimates, up to half of cancer patients suffer from depression at some point in their illness.[28] And not without reason: these patients face uncertainty about their life, and this often results in depression or anxiety.[46]

Many cancer patients with depression also have insomnia.[28] Indeed, patients with persistent insomnia are at greater risk of developing psychological disorders such as depression and anxiety.[47]

In a survey of cancer patients, insomnia symptoms were more often attributed to thoughts or concerns about health, family, friends, the cancer diagnosis, and finances than to the actual physical effects of cancer.[48]

CANCER TREATMENT AND INSOMNIA

Many cancer patients experience sleep disturbances even before starting treatment.[49] Liu et al[50] showed that, in 76 women about to undergo chemotherapy for breast cancer, those who already had sleep disturbances, fatigue,

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TABLE 2

Cancer treatment as a cause of insomnia

Cancer treatment	Mechanism of sleep disturbance	Examples
Chemotherapy	Cancer-related fatigue, daytime sleepiness, mood disorders, restless leg syndrome	Taxanes, platinum-based chemotherapy
Radiation therapy	Daytime sleepiness, radiation-induced emesis causing difficulty sleeping, fatigue	
Hormonal therapy	Hot flashes, night sweats, menopause-like symptoms, anxiety	Antiandrogens (eg, leuprolide acetate, flutamide), antiestrogens (eg, tamoxifen)
Biological therapy	Daytime fatigue, malaise	Interferons for malignant melanoma
Corticosteroids	Increase in serum cortisol	Prednisone, dexamethasone
Bone marrow transplantation	Severe anemia causing daytime fatigue and restless leg syndrome	
Surgery	Pain, recovery from surgery, surgery with aesthetic or functional impairments	Mastectomy, debulking surgeries

and depression had more problems, and more severe problems, during chemotherapy.

Radiation therapy and chemotherapy have been reported to cause or precipitate insomnia (TABLE 2).[8,13]

Opioid-induced sleep-disordered breathing should be managed in partnership with a sleep specialist

Hormonal therapy and biological therapy can also cause or worsen preexisting insomnia.[51,52] For example, androgen deprivation therapy for prostate cancer and hormonal therapy for breast cancer are often associated with sleep problems.[49,50] Possible mechanisms of insomnia include hot flashes, night sweats, and anxiety caused by such treatments. Biological agents such as interferons, interleukins, and tumor necrosis factor (TNF) alpha, which are often used to treat malignant melanoma, can affect the sleep-wake cycle, leading to insomnia.[53]

Corticosteroids sharply raise serum cortisol levels, which can lead to insomnia. Cancer patients receiving dexamethasone to prevent radiation-induced emesis experienced more insomnia than patients who did not receive dexamethasone.[54]

IMMUNOLOGIC BASIS OF INSOMNIA IN CANCER PATIENTS

Cancer cells produce inflammatory cytokines such as interleukin 1 (IL-1), interleukin 6 (IL-6), and TNF alpha, and inflammation plays a role in tumor progression and possibly tumorigenesis.[55]

Specific cytokines also help regulate the sleep-wake cycle. Levels of IL-6 and TNF alpha peak during sleep, and daytime IL-6 levels are inversely related to the amount of nocturnal sleep.[56] Vgontzas et al[57] showed that although mean levels of 24-hour IL-6 and TNF alpha secretion were not significantly different in patients with insomnia vs healthy controls, chronic insomnia was associated with a shift in IL-6 and TNF alpha secretion from nighttime to daytime.[57]

Cancer and its treatment can affect secretion of the cytokines that play a role in the sleep-wake cycle. Thus, the sleep disturbances associated with cancer may also be related to the abnormalities in cytokine levels caused by either cancer or its treatment.

Mills et al[58] found that inflammatory markers such as vascular endothelial growth factor and soluble intercellular adhesion molecule-1 were significantly elevated during chemotherapy in breast cancer patients, and the elevated vascular endothelial growth factor levels were associated with poorer sleep during treatment.

Further research is warranted to establish causality, to help us understand the mecha-

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nisms of insomnia and other cancer symptoms, and to develop new treatments for these complaints.

POOR SLEEP AND CANCER RISK AND OUTCOMES

Sleep disturbances have negative health consequences in cancer. Their impact ranges from plausible carcinogenesis to affecting the course of the disease and cancer survival.

Poor sleep and risk of cancer

Epidemiologic studies have examined a possible link between circadian rhythm disruption and breast cancer risk, using both direct measures such as melatonin levels and indirect measures such as sleep duration and shift work. (Melatonin production is related to sleep duration, and night-shift work leads to disruption of sleep pattern and quality of sleep, thus lowering melatonin levels.[59])

The findings were mixed. Breast cancer risk was significantly and inversely associated with urinary melatonin levels (6-sulfatoxymelatonin) in the Nurses' Health Study II,[60] but not in the Guernsey III study in the United Kingdom.[61] Breast cancer risk was significantly lower with longer sleep duration in Finnish women[62] and in Chinese women in Singapore,[63] but not in American women.[64,65] Results of three cohort studies[66–68] and two case-control studies[69,70] suggested a higher breast cancer risk in women who work evening or overnight shifts. Shorter sleep duration was associated with a higher risk of colorectal adenomas.[71]

These studies make a strong case for an association of cancer with circadian rhythm disruption and shorter sleep duration, possibly from an effect on melatonin levels. However, one should be cautious in interpreting epidemiologic studies: although they show sleep disturbances to be associated with cancer risk, they do not establish causality.

Insomnia and cancer outcomes

Evidence is growing that sleep disturbances may affect compliance with treatment, immune function, and outcomes—including survival—in cancer patients.[23,24]

In patients newly diagnosed with various types of cancer, Degner and Sloan[72] showed that those who suffered from insomnia, nausea, poor appetite, and pain had a lower survival rate at 5 years, independent of the cancer stage. However, no separate analyses were performed to examine the specific influence of insomnia on cancer survival.

Thompson and Li[73] analyzed data from 101 breast cancer patients with available Oncotype DX recurrence scores (a proprietary genetic test performed on tumor tissue that predicts the likelihood of recurrence). The scores were strongly correlated with average hours of sleep per night before breast cancer diagnosis, with fewer hours of sleep associated with a higher (worse) score.

Since these studies were retrospective and merely suggest associations, prospective studies, using more standardized questionnaires and objective measures, are needed to establish causality and to further our understanding of the mechanisms involved.

HELPING CANCER PATIENTS SLEEP BETTER

Insomnia is generally diagnosed with a thorough history that includes sleep, medical issues, substance use, and psychiatric issues. The sleep history should include specific insomnia-related complaints, presleep conditions and habits, sleep-wake habits, other sleep-related symptoms, and daytime consequences. To obtain the information, one can use questionnaires, sleep logs, psychological screening tests, and bed-partner interviews.[74]

Managing insomnia involves both pharmacologic and nonpharmacologic treatment

Managing insomnia involves both pharmacologic and nonpharmacologic treatment. It is also important to treat the associated disorders such as depression and anxiety disorders that often accompany insomnia. Long-term management of cancer patients should not be limited to surveillance of cancer but should also involve aggressive treatment of clusters of symptoms such as insomnia, cancer-related fatigue, and pain to yield better long-term quality of life.[75–77]

Nonpharmacologic treatment: Cognitive-behavioral therapy

Nonpharmacologic interventions use psychological and behavioral therapies. The American Academy of Sleep Medicine guidelines

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TABLE 3

Major components of nonpharmacologic therapy for insomnia

Therapy	Objective	How to practice
Stimulus control	Associate the bed and bedroom with sleep Establish a consistent sleep-wake schedule	Limit activities in bed Go to bed only when sleepy Get out of bed if unable to sleep in 15–20 minutes and do something relaxing
Cognitive-behavioral therapy	Alter the patient's irrational and negative beliefs and attitudes about sleep	Cognitive therapy aims at changing the irrational beliefs relating to sleep and reframe it into more appropriate thoughts; usually prescribed by a psychotherapist Behavior therapy includes stimulus control, sleep restriction, and sleep hygiene education
Relaxation training	Reduce somatic tension and thoughts that prevent the patient from sleeping	Progressive muscle relaxation (the patient can learn to relax one muscle at a time until the entire body is relaxed)
Sleep restriction	Improving sleep efficiency	Restrict the time spent in bed to the actual amount of time spent asleep, then gradually increase the sleep time as sleep efficiency improves
Paradoxical intention	Eliminate the performance anxiety limited to sleep-initiation insomnia	The patient is instructed to stay awake and to avoid any efforts to fall asleep
Biofeedback	Reduce somatic arousal	Visual or auditory feedback

INFORMATION OBTAINED FROM MORGENTHALER T, KRAMER M, ALESSI C, ET AL. PRACTICE PARAMETERS FOR THE PSYCHOLOGICAL AND BEHAVIORAL TREATMENT OF INSOMNIA: AN UPDATE. AN AMERICAN ACADEMY OF SLEEP MEDICINE REPORT. SLEEP 2006; 29:1415–1419.

recommend cognitive behavioral therapy for all patients with insomnia, either alone or in combination with hypnotic medications.

Cognitive-behavioral therapy for insomnia includes various components that help the patient learn coping skills and ways to prevent or mitigate the severity of future episodes (TABLE 3). Various randomized controlled trials found it to be effective for treating insomnia in the general population.[77–79]

Several studies found that cognitive-behavioral therapy for insomnia was effective in cancer patients, not only improving sleep quality but also decreasing psychological distress, resulting in better overall quality of life.[80,81]

Savard et al[81] conducted a randomized controlled trial of cognitive-behavioral therapy for insomnia in 57 patients with breast cancer, examining subjective and objective sleep measures, psychological functioning, quality of life, and immunologic responses. They found significant improvements in sleep efficiency, mood, quality of life, depression, anxiety, and need for sleep medications. Improvements in subjective sleep measures persisted on 12-month follow-up.

Berger et al,[82] in another randomized controlled trial, assessed behavioral therapy using stimulus control, modified sleep restriction, relaxation therapy, and sleep hygiene in breast cancer patients receiving adjuvant chemotherapy. Behavioral therapy improved sleep quality over time, as measured by the Pittsburgh Sleep Quality Index.

Espie et al[83] evaluated the effect of cognitive-behavioral therapy on prostate, colorectal, gynecologic, and breast cancer patients, with similar results.[83]

Cognitive-behavioral therapy is at least as effective as drug therapy for insomnia in the general population. In the limited studies done in cancer patients, it has been shown to

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TABLE 4

Drugs used for insomnia

Class	Additional properties	Examples
Nonbenzodiazepine hypnotic agents	Few adverse effects	Zolpidem, zaleplon, eszopiclone
Benzodiazepines	Anxiolytic	Clonazepam, lorazepam
	Hypnotic	Temazepam, flurazepam
Tricyclic antidepressants	Antidepressant	Amitriptyline, nortriptyline
Second-generation antidepressants	Antidepressant and may aid in gaining weight	Trazodone, mirtazapine
Other antidepressants	Antidepressant	Doxepin
Antipsychotics	Mood-stabilizing effect	Olanzapine, risperidone
Antihistamines	Antipruritic	Diphenhydramine, hydroxyzine
Psychostimulants	Reduce cancer-related fatigue	Methylphenidate, modafinil
Neuroleptics	Antiemetic	Chlorpromazine, thioridazine
Melatonin agonists	Fewer adverse effects	Ramelteon

be effective irrespective of the type of cancer and is associated with better long-term outcomes. It diminishes the distress associated with early insomnia, can reduce anxiety, and can promote sleep.

A National Institutes of Health conference on insomnia concluded that cognitive-behavioral therapy is at least as effective as medications for brief treatment of chronic insomnia and that its beneficial effects, in contrast to those produced by medications, may last beyond the termination of treatment.[84]

It is important to think about numerous factors when considering options such as cognitive-behavioral therapy, as patients with cancer have different complications that may affect sleep quality, such as cancer-related fatigue, cancer-related depression, psychological reactions to the disease, side effects of treatment, and cancer-related pain. These need to be addressed as well.

If cognitive-behavioral therapy is not available, self-help interventions (eg, written material, videos, television and Internet resources) can be used. These have several advantages over professionally administered interventions, including greater accessibility, less burden for the patient, and lower cost. Research is under way evaluating this approach in cancer patients.[85]

If cognitive-behavioral therapy is not available, self-help interventions—written material, videos, and TV, and Internet resources—can be used

Drug therapy

The focus of therapy should be to treat underlying disorders that may be causing or contributing to insomnia. However, a substantial number of patients may need to be assessed for pharmacotherapy for insomnia.

Sleep problems in the general population are commonly treated with drugs, and most of the recommendations in cancer patients are based on experience in the general population. However, sleep medications should be used cautiously in cancer patients, since to our knowledge there have been no studies of these agents in patients with cancer.

Side effects also need to be considered. For example, sleep medications can profoundly worsen cancer-related fatigue.

Hypnotics are often prescribed for cancer patients.[86,87] A study in five major oncology centers showed that about half of the 1,500

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patients were prescribed at least one psychotropic drug.[86] In this study, hypnotics were the most frequently prescribed drugs, accounting for 48% of total prescriptions, and 44% of the psychotropic prescriptions were written for sleep.

Benzodiazepine receptor agonists such as zaleplon, zolpidem, and eszopiclone can be used for problems with falling asleep and staying asleep.[88,89] They are better tolerated than older, long-acting benzodiazepines,[90] which can cause alterations in sleep-cycle architecture or rebound insomnia. The earlier agents can also cause adverse effects such as tolerance, drowsiness, and cognitive impairment.

A National Institutes of Health conference stated that benzodiazepine receptor agonists are efficacious in the short-term management of insomnia and that their adverse effects are much less frequent and severe than those of the benzodiazepines or other sedating drugs.[84] It also stated that all antidepressants, antihistamines (H1 receptor antagonists), and antipsychotics have potentially significant adverse effects that raise concerns about their risk-to-benefit ratio and their suitability as treatment for chronic insomnia.

Benzodiazepines are commonly prescribed for insomnia. They increase sleep efficiency, decrease arousals, and increase stage 2 sleep.

Melatonin receptor agonists have been approved by the US Food and Drug Administration for treating insomnia. A recent meta-analysis of eight studies in healthy patients showed improvements in subjective and objective sleep outcomes with the use of ramelteon.[91] The dosages primarily used were 4 to 32 mg. However, most of the studies used a dosage of 4 to 8 mg.

Antidepressants. Some of the antidepressants are also used for insomnia, but they can cause daytime fatigue.

Mirtazapine was shown to be effective for insomnia and coexistent mood disorder in cancer patients, but larger trials are needed.[92]

A recent clinical trial with secondary data analyses evaluated the effect of paroxetine on insomnia, depression, and fatigue in patients with cancer. Paroxetine significantly reduced insomnia in both depressed and nondepressed patients after 2 to 3 weeks of treatment.[93]

TABLE 4 summarizes classes of drugs used for insomnia and their additional therapeutic properties.

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