

# Pathogenesis and Management of Cancer-Related Insomnia

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Insomnia (defined as a subjective complaint of inadequate nocturnal sleep) is the most common sleep disorder reported by cancer patients.<sup>1</sup> Although alterations in sleep patterns are endemic among this population,<sup>2</sup> sleep problems are rarely assessed in a typical patient evaluation. Furthermore, patients often fail to mention symptoms to their caregiver, and when sleep is assessed, it is usually in the form of a single question.<sup>3,4</sup> As a result, insomnia is often unrecognized and untreated.<sup>5-7</sup>

Sleep deprivation has been associated with a decline in cognitive function, inability to engage in work or recreational activities, loss of hedonic capacity, a sharp decline in quality of life, and alterations to immune and neuroendocrine function.<sup>8-11</sup> Furthermore, sleep deprivation often persists long after treatment for cancer is completed.

## Scope of the Problem

In healthy populations, the incidence of some form of insomnia is about 33%, whereas insomnia severe enough to interfere with daytime functioning is estimated to affect about 10%–15% of the general population.<sup>12-14</sup> Insomnia is a heterogeneous condition that can be symptomatic of an underlying emotional, medical, or substance disorder.<sup>7</sup> It can also be an independent disorder with no known etiology, or so-called primary insomnia. Figure 1 illustrates the main correlates associated with disturbed sleep patterns in cancer patients.

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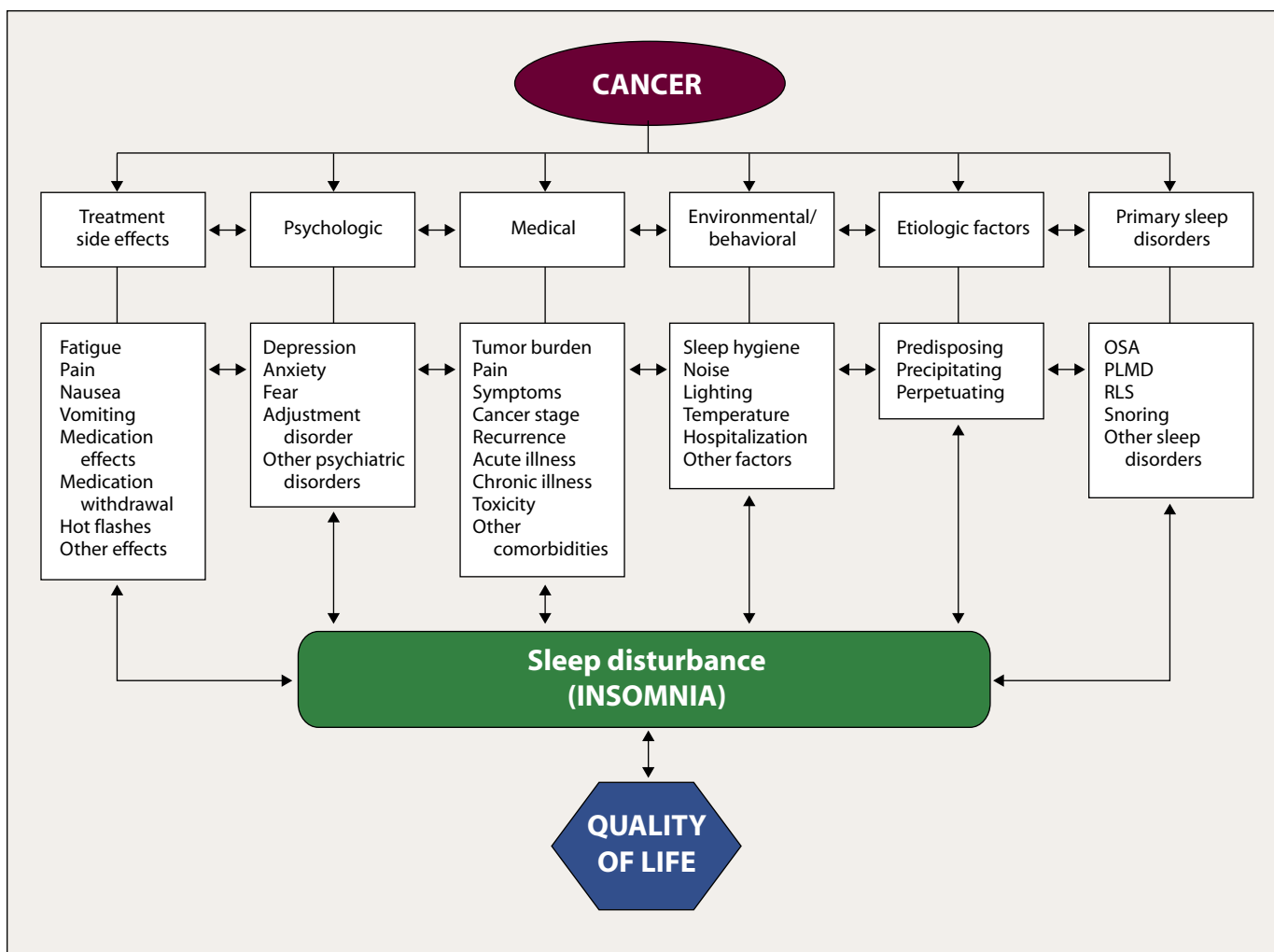
**Abstract** Insomnia is the most common sleep disorder reported by cancer patients. Oncologists have noticed that alterations in sleep patterns are endemic among their patients, yet sleep problems are rarely assessed in a typical patient evaluation. Other concerns, such as morbidity and mortality, appear to take precedence. The cause of chronic sleep difficulties is multifaceted and up until recently, little attention has been given to the potential factors associated with the pathogenesis of cancer-related insomnia. The unique contributions of psychologic, medical, treatment side effects, environmental, behavioral, and pharmaceutical pathways on cancer-related insomnia cannot be ignored. This paper explores an overview of the incidence and severity of sleep disturbance in cancer patients, a review of the mechanisms of sleep, and the potential factors associated with the pathogenesis of cancer-related insomnia. Nurses, physicians, and other healthcare providers are in a unique position to greatly improve the quality of sleep in cancer patients. Cancer patients face many challenges; sleep problems do not have to be one of the necessary consequences associated with the cancer experience.

The prevalence, type, and severity of sleep complaints in a cancer population have been difficult to judge,<sup>15</sup> with prevalence estimates ranging from 24% to 95%.<sup>16,17</sup> Most studies estimate that approximately half of patients with cancer suffer from insomnia, with 23%–44% reporting insomnia complaints up to several years following their diagnosis and treatment.<sup>6,18,19</sup> Unfortunately, there are no standard quantitative criteria to diagnose insomnia, and standardized and operationally defined criteria are lacking,<sup>5,7</sup> which contributes to the variability in research findings across both subjective and objective studies.

## REVIEW OF SLEEP STAGES

Sleep patterns are defined by their architecture and circadian factors. Sleep architecture refers to the two stages of sleep, non-rapid eye movement (NREM) sleep and dream or rapid eye movement (REM) sleep. Circadian factors regulate the daily, 24-hour rhythm of sleeping and waking. Disruptions in both architecture and circadian factors

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**Figure 1** Potential Factors Contributing to the Pathogenesis of Cancer-Related Insomnia

Abbreviations: OSA = obstructive sleep apnea; PLMD = periodic limb movement disorder; RLS = restless leg syndrome

account for the majority of sleep disturbances encountered in the context of cancer.

### Diagnosis and Classification

In a cancer patient population, insomnia complaints are often secondary to underlying psychiatric and medical conditions, and these conditions should be assessed and treated as a first measure.<sup>20</sup> The International Classification System of Sleep Disorders (ICSD)<sup>21</sup> and the Diagnostic Statistical Manual, Version IV (DSM-IV)<sup>22</sup> are the two classification systems currently used for diagnosing insomnia. Table 1 presents a definition of insomnia according to combined criteria of the DSM-IV and the ICSD and those generally used in clinical research.<sup>5,23</sup>

Insomnia commonly has been classified by its duration<sup>24</sup>:

- Transient, defined as less than 2 weeks;
- Short-term, lasting between 2 and 4 weeks; and
- Chronic, defined as lasting more than 4 weeks.

Timing of the sleep disturbance is important for classifying insomnia into three types<sup>23,25</sup>:

- Delayed sleep onset (difficulty falling asleep);

- Impaired sleep continuity (difficulty staying asleep); and
- Early-morning awakening.

In each of these types of insomnia complaints, the key feature is that the individual has difficulty initiating and/or returning to sleep. It is essential that clinicians differentiate between patients who are naturally short sleepers (ie, less than 6 hours) from those whose sleep has been shortened and fragmented from psychologic, medical, pharmaceutical, environmental, and/or behavioral factors. The complaint of impaired functioning is a good clue to help distinguish short sleepers from truly disturbed sleepers.

Keep in mind that a diagnosis of cancer may aggravate an already present insomnia complaint. The two common types of insomnia disorders diagnosed within a cancer population are adjustment and psychophysiological sleep disorders.

Adjustment sleep disorder is a condition in which an individual has experienced a significant life stressor (such as death of a loved one or the diagnosis of a life-threatening illness) that interferes with sleep. This type of sleep disorder is more commonly transient and generally abates within 1 month.

**Table 1**  
Insomnia Diagnostic Criteria

Difficulty sleeping characterized by any or all of the following: <ul style="list-style-type: none"> <li>• difficulty falling asleep (ie, greater than 30 minutes to fall asleep);</li> <li>• difficulty maintaining sleep (ie, greater than 30 minutes of nighttime awakenings);</li> <li>• waking up too early; or</li> <li>• complaint of non-refreshing sleep or poor sleep quality.</li> </ul>
Sleep disturbance must cause significant impairment in daytime functioning or marked distress.
Sleep disturbance occurs at least 3 nights per week.
Sleep duration of less than 6 hours per night.
Sleep difficulty must occur despite adequate opportunity for sleep.

Adapted from Savard and Morin<sup>5</sup>

However, it can progress to chronic insomnia, often accompanied by depression. In comparison, psychophysiological insomnia is a sleep disorder that results from the presence of heightened arousal in which somatized tension and learned sleep-preventing associations (eg, nervousness, anxiety, ruminative thoughts) interfere with nocturnal sleep.

The majority of cancer patients suffer from secondary insomnia, that is, rather than being a long-standing, premorbid problem, insomnia emerges as a psychological or physiological side effect of diagnosis and/or treatment. Obviously, sleep disruptions may be attributable to many factors in a cancer patient: pain, side effects of treatment, or psychological factors such as depression and anxiety (Figure 1).

### ETIOLOGIC FACTORS

Sources of sleep disturbance in cancer patients are many, varied, and complex. It is helpful to think of these sources in terms of predisposing, precipitating, and perpetuating factors.<sup>5,26</sup> A general list of these factors is shown in Table 2.<sup>5</sup>

Significant factors in continuing sleep problems are patients' faulty beliefs and attitudes about sleep and sleep disturbance.<sup>5</sup> Many patients believe that 8 hours of continuous sleep each night is necessary to maintain daily functioning. Actually, the normal range of sleep time among healthy individuals is from 6 hours to 10 hours or more.<sup>27</sup> Further, there appears to be no evidence that occasional loss of sleep has any lasting effect. Nevertheless, sleep disturbance often elicits anxiety, leaving patients lying in bed worrying about whether they will get to sleep or get enough sleep, which further contributes to sleep disturbance.

### RISK FACTORS

Insomnia is more common among females, older individuals, and the depressed or anxious.<sup>25</sup> Additionally, low socioeconomic status, chronic medical illness, low level of education, recent life stressors, and the use of alcohol are also associated with insomnia complaints.

### PSYCHOLOGIC FACTORS

Clinically significant symptoms of depression are present in up to half of cancer patients at some time during their disease

**Table 2**  
Predisposing, Precipitating, and Perpetuating Factors Associated With Sleep Disturbance in Cancer Patients

<b>Predisposing Factors</b>
Being female
Older age
Hyperarousability trait
Personal or family history of sleep disorder
Personal or family history of mood or anxiety disorder
Current diagnosis of mood or anxiety disorder
<b>Precipitating Factors</b>
Psychologic distress in response to cancer diagnosis and/or treatment
Immunologic and thermoregulatory changes
Bone marrow transplantation
Pain
Gastrointestinal distress
Respiratory distress
Chemotherapy
Radiation therapy
Hormonal therapy
Menopausal symptoms (night sweats)
Medications for treatment side effects
Hospitalization
Environmental factors (noise, light, exogenous sleep disturbance)
<b>Perpetuating Factors</b>
Maladaptive behaviors, including excess time in bed, daytime napping, reduced daily activity, frequent alterations in sleep and wake times, long-term use of medications or use of inappropriate medications
Maladaptive cognitions, including unrealistic sleep expectations, false perception of sleep time and quality, false perception of daytime impairments, difficulty discerning causes of daytime fatigue

Adapted from Savard and Morin<sup>5</sup>

course,<sup>8,28</sup> yet only 5%–6% of cancer patients are treated with antidepressant medication. Sleep disturbances are pathognomic in depression. Anxiety is also prevalent in cancer patients, with some significant symptoms occurring in up to 50% of this population.<sup>29,30</sup> The American Psychiatric Association has recently added cancer as a traumatic event capable of eliciting symptoms of post-traumatic stress disorder.<sup>22</sup> This type of anxiety disorder is typically associated with sleep initiation and maintenance difficulties and with vivid nightmares about the traumatic event.<sup>31</sup>

### MEDICAL FACTORS

The extent of sleep difficulties has been shown to vary with different cancer types. For example, one study measuring sleep problems in lung cancer patients, breast cancer patients, insomniacs, and healthy controls found that lung cancer patients had greater decreased sleep efficiency (ratio of time spent sleeping to time spent in bed) compared with breast cancer patients or controls. Lung cancer patients also had longer sleep onset latencies, more fragmented sleep, and more stage 1 sleep (light sleep) than breast cancer patients or controls.<sup>32</sup> In another study of sleep and fatigue complaints in a heterogeneous sample of patients, those with lung cancer

### Case History 1: Behavioral Treatment of Psychophysiological Insomnia

Mrs. C, a 43-year-old homemaker and mother of three children, was referred for insomnia after failed benzodiazepine treatment prescribed by her oncologist. Mrs. C reported no significant history of disordered sleep prior to her cancer diagnosis at age 41. Patient reported ending cancer treatment (chemotherapy and radiation therapy) 7 months ago. Patient denied experiencing a significant psychiatric history but acknowledged experiencing depression and anxiety when initially diagnosed. The depression alleviated within 2 months, but Mrs. C reported feeling anxious and tense at night and experiencing ruminative thoughts about her health and its impact on her family. Mrs. C also stated that she was very focused on her “lack of sleep” and was constantly “clock-watching” during the night. On nights when sleep was unlikely, she reported getting up and turning on the lights in her home and would “clean house” for several hours. She also reported concerns that her sleep deprivation would somehow “cause” her cancer to recur.

Mrs. C was requested to complete 2 weeks of sleep logs prior to her clinical visit. Review of these sleep logs revealed a sleep efficiency of 78% (> 85% is within normal limits). She also engaged in poor sleep hygiene behaviors, which were mentally and physically stimulating (ie, watching television in bed, reading in bed, worrying in bed, exposure to bright light during the night, and physical activity—house cleaning).

A diagnosis of psychophysiological insomnia was made, and Mrs. C's presleep and nighttime behaviors were examined in detail. She was prescribed stimulus control therapy (including education about proper sleep hygiene behaviors) and sleep restriction treatment. Mrs. C was advised to keep a “worry journal” because she was spending excessive amounts of time worrying and ruminating about her health and its impact on her family. She was instructed to write down her worries and construct possible solutions for a minimum of 30 minutes (not to exceed 60 minutes) every night, 2 hours before bedtime. She was also instructed to eliminate watching television or reading in bed, which were two activities that she enjoyed. Because reading was an enjoyable and mentally stimulating activity, she was advised to stop reading 1 hour before bedtime. She was encouraged to create a presleep bedtime routine consisting of calming activities (eg, listening to a 30-minute progressive muscle relaxation or guided imagery tape, praying). At bedtime, she was requested to set her alarm clock and turn it toward the wall to eliminate clock watching. Sleep restriction treatment limited the amount of time spent in bed and assisted Mrs. C in maintaining a regular sleep schedule.

Mrs. C regained her precancer sleep patterns within 3 days, and the sleep restriction treatment was quickly tapered. She typically falls asleep within 15 minutes and remains asleep throughout the night. If she awakens during the night, she is able to return to sleep quickly. She reported complete satisfaction with this regimen and continues these adaptive sleep behaviors.

had the highest prevalence of sleep-related problems.<sup>33</sup>

One source of both nighttime sleep disturbance and daytime fatigue is interference with respiration.<sup>34</sup> Respiratory problems are common in lung cancer patients,<sup>16</sup> but other

types of cancers interfere with breathing as well. Patients with obstructions to airway passages, such as mucosal hemangioma patients, may develop obstructive sleep apnea.<sup>35</sup> Sleep disturbance can also be attributed to coughing and alterations in immunologic function,<sup>36</sup> which in turn can be associated with changes in sleep patterns.<sup>4</sup> Pain can manifest in many ways and obviously can disrupt sleep.<sup>37–39</sup>

### MEDICATIONS

Medications, such as corticosteroids, also are known to contribute to sleep problems.<sup>40</sup> Table 3 illustrates common cancer treatment medications that can elicit or aggravate insomnia.<sup>41,42</sup>

Analgesic medications—especially opioids and their derivatives—often useful in initial restoration of nighttime sleep<sup>43</sup> may also eventually contribute to sleep disruption.<sup>44</sup> Morphine can cause sedation and daytime sleepiness, disrupting sleep patterns and circadian rhythms. Long-term opioids also can increase the incidence of respiratory disturbances. Myoclonus, too, may occur,<sup>45</sup> typically during sleep initiation.

Antidepressants also may increase the risk of myoclonus, or periodic leg movements associated with arousal.<sup>46</sup> Selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs) are associated with disruptions in sleep architecture because the majority of these medications are stimulants. Patients taking SSRIs and MAOIs have shown increases in light sleep (stage 1 and 2 sleep) and decreases in deep sleep (stage 3 and 4 sleep), as well as an increase in REM latency.<sup>47,48</sup> However, the majority of cancer patients taking these medications report improved subjective sleep quality.<sup>49</sup> The reasons for this discrepancy are not entirely clear. Other antidepressant medications have similar paradoxical findings.<sup>50</sup>

Short-acting amphetamines are also prescribed as antidepressant agents.<sup>48,50</sup> One might imagine that the use of stimulants would always be contraindicated in insomnia because they are known to disrupt sleep cycles. However, used judiciously, stimulants may have a salubrious effect on sleep by treating daytime fatigue and sedation. If patients can maintain alertness during the day, they are less likely to nap, and therefore more likely to sleep at night, helping to reset their 24-hour sleep/wake cycle. To achieve this effect, the stimulant should be given in small doses, early in the day.

Lastly, if it is determined that a patient's sleep disturbance is secondary to depression, treatment should be directed at the affective illness, and the use of sedating tricyclic antidepressants is recommended. Table 4 illustrates commonly prescribed psychotropic medications and their effects on sleep.<sup>2,51</sup>

### BENZODIAZEPINES

Many of the pharmaceutical agents used in the treatment of insomnia have significant side effects. Benzodiazepines, although still the first-line treatment for many causes of insomnia, have potential addictive properties, including tolerance.<sup>52,53</sup> In addition, there is evidence that benzodiazepines only slightly reduce sleep latency and significantly increase

**Table 3**  
Common Agents That May Cause Insomnia

Central nervous system stimulants (eg, amphetamines)
Caffeine
Diet pills
Dietary supplements used in weight loss and appetite suppression
Sedatives and hypnotics (eg, glutethimide, benzodiazepines, pentobarbital, chloral hydrate, secobarbital sodium, amobarbital sodium, other agents)
Cancer chemotherapeutic agents (eg, antineoplastics)
Anticonvulsants
Adrenocorticotropins
Antidepressants and anxiolytics (including stimulating tricyclics and monoamine oxidase inhibitors)
Antihypertensives (eg, propranolol, atenolol, methyl dopa)
Alcohol
Hormones (eg, oral contraceptives, thyroid preparations, cortisone)
Bronchodilators
Xanthine derivatives (eg, theophylline)
Decongestants (eg, phenylpropanolamine and pseudoephedrine)
Withdrawal from central nervous system depressants, barbiturates, opioids, glutethimide, chloral hydrate, methaqualone, ethchlorvynol, or alcohol
Antihistamine sedatives (over-the-counter and prescription drugs)
Benzodiazepines
Major tranquilizers
Antidepressants (tricyclics and monoamine oxidase inhibitors)
Illicit drugs (eg, marijuana, cocaine, phencyclidine, opioids)

sleep duration. There is no corresponding change in REM latency, relative total REM and NREM sleep, sleep efficiency, or number of nighttime awakenings.<sup>54</sup> Further, discontinuation of benzodiazepines is associated with a rebound effect, where insomnia returns to higher than baseline levels for 1–2 nights following acute medication discontinuation. It is characterized by an increase in sleep latency onset and poor sleep efficiency.<sup>55</sup> The immediate side effects of benzodiazepines include a next day “hangover” effect, motor slowing, and cognitive difficulties.<sup>56</sup>

#### CHEMOTHERAPY AND RADIATION TREATMENT

Cancer chemotherapy in general and antimetabolites and cytotoxic agents in particular are associated with sleep disruption<sup>57–59</sup> and greater fatigue during the daytime.<sup>60,61</sup> Radiation therapy, too, is commonly associated with increases in daytime fatigue and somnolence.<sup>62</sup> In a pilot study by Miaskowski and Lee,<sup>63</sup> radiation therapy resulted in declines in sleep efficiency and more time spent awake. These patients reported higher levels of daytime dysfunction.

Chemotherapy and hormonal therapy can cause hormonal changes in women, as can surgical castration with bilateral oophorectomy, leading to premature menopause or aggravated menopausal symptoms.<sup>19,64</sup> Vasomotor symptoms, such as hot flashes, significantly interfere with perceived sleep quality and delays in sleep onset.

**Table 4**  
Psychotropic Medications and Sleep

MEDICATION	SEDATIVE EFFECTS
Amitriptyline	++++
Doxepin	++++
Trazodone	++++
Mirtazapine	++++
Olanzapine	++++
Quetiapine	+++
Nefazodone	+++
Imipramine	++
Venlafaxine	++
Nortriptyline	++
Sertraline	++/+
Buspirone	+
Paroxetine	+
Desipramine	+/-
Clomipramine	+/-
Protriptyline	-
Fluoxetine	-
Bupropion	-
Phenelzine	-
Tranlycypromine	-

#### GASTROINTESTINAL PROBLEMS

Gastrointestinal distress associated with cancer and cancer treatment also may interfere with sleep.<sup>40,65</sup> In addition, there is significant evidence that medications given for nausea and emesis may contribute to sleep disturbance. These medications include corticosteroids as well as antiemetics.<sup>66</sup>

#### EFFECTS OF HOSPITALIZATION, AUDITORY AND LIGHT DISTURBANCES

During hospitalizations cancer patients’ sleep is interrupted<sup>67</sup> for a variety of patient-care activities as well as by auditory and light disturbances. Many patients find these nighttime disruptions highly stressful<sup>68</sup> and will sleep during the day to compensate for the loss of nocturnal sleep. As a result, when patients go back home, they find their sleep rhythms adapted to a hospital schedule and experience difficulty re-adapting these rhythms to a regular sleep schedule.

#### PATIENT CONTRIBUTORS TO SLEEP DISTURBANCE

Patients may also contribute to their sleep disturbance. For instance, most patients lack knowledge about foods, drinks, medications, and physical activities with psychostimulant properties that can interfere with sleep. Patients may also overuse “over-the-counter” or “herbal” remedies. These are examples of poor sleep hygiene behaviors.<sup>69,70</sup> A general guideline is to educate patients about the bedroom environment, that it is only for sleep and intimate activities. It should be considered a safe haven and an environment that is conducive to sleep. Table 5 lists examples of important “presleep behaviors” that enhance and minimize sleep disturbance in



### Case History 2: Pharmacologic Treatment of Substance-Induced Mood Disorder

Mr. P, a 55-year-old athletic coach, was referred by his oncologist for sleep disturbance. He was diagnosed with non-Hodgkin's lymphoma and began chemotherapy. Upon interview, he reported a 5-month history of difficulty initiating and maintaining sleep that worsened in the last month. He began chemotherapy 3 months ago and has been taking steroids as part of his treatment protocol. He was taking zolpidem (30 mg at bedtime) and clonazepam (2 mg at bedtime) for his sleep complaints with no relief. He reported experiencing heart palpitations and feeling "edgy" since his physician increased his zolpidem dosage.

Physically, he appeared tired, anxious, and focused on his "lack of sleep" and impaired daytime functioning. He acknowledged experiencing mild depression, which appeared related to his lack of sleep and energy. He reported engaging in very poor sleep hygiene activities (eg, worrying in bed, clock watching, reading, sleeping during the day for several hours, etc.) and spending excessive time in bed "trying to make up for lost sleep." Based on his presentation, he was diagnosed with a substance-induced mood disorder, in which insomnia was secondary to the mood disorder. However, his poor sleep hygiene behaviors also negatively influenced his ability to sleep and stay asleep. He discontinued taking zolpidem and clonazepam. The heart palpitations and "edginess" immediately disappeared after discontinuation of zolpidem.

Mr. P was prescribed olanzapine (10 mg at bedtime), and during times when his steroid dosage was increased, the olanzapine dose was titrated (20 mg at bedtime). He was also advised to keep a regular sleep schedule that was to be maintained even on weekends. Early-morning exercise was added to his daily schedule. This regimen improved his sleep markedly during cancer treatment; he maintained this schedule for 3 months. After treatment ended, he was tapered off olanzapine and reported falling asleep within 20 minutes and remaining asleep throughout the night. He reported complete satisfaction with this regimen.

cancer patients. Insomnia complaints can often be corrected by implementing these "proper" sleep hygiene behaviors.

#### PRIMARY SLEEP DISORDERS

It is important to differentiate other primary sleep disorders (eg, obstructive sleep apnea, restless leg syndrome, periodic leg movements) that may be either masking as insomnia or exacerbated by the disease. Obstructive sleep apnea, snoring, restless legs, and periodic leg movements are examples of some sleep disorders that cause fragmented sleep. It is essential to rule out the influence of primary sleep disorders that can cause sleep disturbance.

#### Assessment

##### PATIENT SELF-REPORT

Clinical interviews are extremely useful in obtaining information on the nature, history, and severity of sleep disturbance.

**Table 5**

#### Sleep Hygiene Behaviors for Cancer Patients

Keep a regular time for going to sleep and waking up (even on week-ends).
Create a bedtime routine; engage in quiet, calming activities.
The bedroom is for sleep and intimate activities only.
Don't lie down for bed until sleepy.
If you don't fall asleep within 15–20 minutes, get out of bed and go into another room and engage in a quiet non-stimulating activity until you are sleepy and then return to bed.
Sleep just long enough.
Regular exercise during the day can deepen sleep; it should be done 4-6 hours before bedtime.
Have a light bedtime snack; avoid heavy foods.
Reduce noise and light level.
Regulate room temperature.
Avoid stimulants—nicotine and food and drinks containing caffeine—4 to 6 hours before bedtime, including chocolate, coffee, and sodas.
Avoid alcohol; it helps you fall asleep but causes awakenings and poor sleep later.
Avoid daytime naps; limit naps to 20 minutes and avoid them after 3 pm.

es.<sup>71</sup> Stepanski et al<sup>72</sup> developed a basic interview questionnaire to evaluate for sleep disorders that may be easily administered by health care professionals or patients themselves (Table 6). In the absence of detailed assessment, patients should be asked about the onset, timing, quantity, and quality of their sleep, as well as their level of fatigue. Examples include:

- "How were you sleeping prior to your cancer diagnosis?"
- "How have you been sleeping lately?"
- "On a scale of one to ten, with one being the worst sleep you can imagine and ten being the most restful and refreshing, how would you rate your sleep on average over the past week?"
  - "Do you have difficulty falling asleep, staying asleep, or both?"
  - "How tired have you been during the day?"
  - "On average, how long does it take you to fall asleep during the night?"
  - "On average, how long are you awake for the entire night?"

Patients identified with a sleep problem should be asked to monitor their sleep in the form of a sleep log. Sleep logs provide the clinician with basic information regarding patients' sleep. However, sleep logs are subject to error because they are subjective ratings of sleep. It is sometimes beneficial to obtain corroborative information about sleep functioning from patients' bed partners. Lastly, assessing the use of alcohol, caffeine, nicotine, and daytime napping are essential in determining whether behavior is the primary determinant of sleep disturbance.

#### PHYSICAL ASSESSMENT

The medical history should include past episodes of sleep problems as well as possible contributing factors (eg, stress, depression, illness, medication, pain, nausea). It should also

**Table 6****Standard Interview Format for the Evaluation of Insomnia**

<b>Definition of the Problem</b>
1. What time do you go to bed? What time is your final awakening?
2. How long does it take you to fall asleep?
3. Do you awaken during the night? If yes, how many times?
4. How much total sleep time do you get?
5. How much total sleep time do you need to feel rested?
6. How long have you had this sleep pattern?
7. What was your sleep like before you developed this problem?
8. What treatments have you tried for your sleep problem?
9. Did any of these treatments help?
<b>Behavioral Insomnia</b>
10. Do you watch television, read, work, or eat during the night? In bed?
11. How do you sleep away from home (eg, on vacation)?
12. Do you fall asleep more easily on the couch than in the bed?
13. Are you easily awakened by noise or light?
14. What do you do while awake at night?
15. Was there a precipitating event when your insomnia first began (eg, hospitalization, stressful event)?
16. Do you take naps during the day?
17. Do you look at the clock during the night?
<b>Cognitive Features</b>
18. Do you feel frustrated or tense when seeing your bed or bedroom?
19. Do you think about your sleep difficulty during the day?
20. Are you afraid of not sleeping? What do you think will happen to you?
21. How does difficulty sleeping affect your life?
<b>Medical</b>
22. Do you have any medical problems? (review of systems)
23. Do you have any pain at night?
24. What medications do you take? What dosages? How often?
<b>Alcohol/Drugs</b>
25. Do you drink alcohol? How much? How often?
26. Do you take any non-prescribed drugs? Diet pills?
27. Have you tried medication for your sleep problem?
28. How much coffee do you drink?
<b>Restless Legs/ Periodic Leg Movements</b>
29. Have you noticed muscle twitches in your legs at night?
30. Do you ever have painful or itching sensations in your legs that prevent you from sleeping?
31. Has your bed partner ever noticed leg movements while you were sleeping?

include a list of current medications, particularly those prescribed or taken over the counter for sleep problems. It is important to determine whether medication-induced sleep disturbance is due to steroids, chemotherapeutic agents, inhalers, or other medications. The medical examination should also include a brief neurologic examination, an oropharyngeal exam to look for anatomical obstructions, as well as urinalysis and a complete blood count.

**DIAGNOSTIC EVALUATION**

The objective measures commonly used for measuring noc-

**Table 6 (cont.)****Standard Interview Format for the Evaluation of Insomnia**

<b>Sleep-disordered Breathing</b>
32. Do you snore?
33. Do you ever awaken gasping for breath?
34. Has your bed partner noticed any unusual breathing pattern?
35. Do you have any difficulty breathing through your nose?
36. Have you ever had surgery on your nose or throat?
<b>Psychiatric</b>
37. Have you ever been treated for emotional or psychologic problems?
38. Have you felt depressed recently?
39. How is your appetite? Has your weight changed lately? How much?
40. Do you have any phobias? Panic attacks?
41. How is your marriage? Does your spouse understand the problems you have been having with your sleep?
42. Do you have an active sex life? Does this affect your ability to sleep?
43. Do you have a stressful job? Stressful life?
<b>Circadian Rhythms</b>
44. Do you find it difficult to get out of bed in the morning?
45. Do you sleep later on weekends (or days off)?
46. What are your work hours?
47. Do you ever change work shifts?
<b>Daytime Sequelae and Miscellaneous Items</b>
48. How does poor sleep interfere with your performance the following day?
49. Is your job performance affected?
50. Do you fall asleep at unexpected times during the day?
51. What would you like to see changed about your sleep?
52. How would improved sleep affect your daytime functioning?
53. Do any family members have insomnia, excessive sleepiness, or another sleep disorder?
54. Do you and your bed partner have similar bedtimes?
55. Does your sleep ever improve under certain circumstances?

Reprinted with permission from Stepanski et al<sup>72</sup>

turnal sleep are polysomnography (PSG) recordings and actigraphy. PSG is not indicated for evaluation of transient insomnia, chronic insomnia, or insomnia associated with psychiatric disorders.<sup>73</sup> However, when a patient reports continued sleep disturbance (especially if the patient is elderly or lives alone) in the absence of contributing behavioral factors, a polysomnogram is useful to determine the causal factors responsible for sleep disturbance (eg, obstructive sleep apnea, periodic leg movements, etc.).

A PSG recording monitors several variables, including brain wave activity, respiratory and cardiac functions, as well as blood-oxygen levels. PSG recordings allow for an in-depth look at all avenues of sleep and are the appropriate tool for diagnosing long-term sleep disorders.

In comparison, actigraphy involves the use of a wrist monitor that records the intensity and frequency of movement. Actigraphy has limitations because it does not allow for calculation of sleep stages and does not discriminate between sleep

**Table 7****Commonly Prescribed Hypnotics, Anxiolytics, and Sedating Antidepressants**

DRUG NAME	BRAND NAME	HALF-LIFE (hr)	USUAL DOSE (mg)
<b>Hypnotics</b>			
Zaleplon	Sonata	1–1.5	5–20
Zolpidem	Ambien	1.5–2.5	5–10
<b>Benzodiazepines</b>			
Triazolam	generic	2–4	0.125–0.25
Oxazepam	generic	5–10	10–30
Temazepam	generic	8–17	7.5–30
Lorazepam	generic	10–20	0.5–2.0
Estazolam	generic	10–24	0.5–2.0
Clonazepam	generic	20–60	0.5–2.0
Quazepam	Doral	40–120	7.5–30
Flurazepam	generic	48–100	15–30
<b>Antidepressants with Sedative Effects</b>			
Trazodone	generic	4–7	50–150
Amitriptyline	generic	14–18	25–75
Doxepin	generic	20–25	75–150
Mirtazapine	generic	20–40	15–45
Olanzapine	Zyprexa	21–54	2.5–10

and lying still while awake. Thus, inaccurate estimates of sleep parameters may result. Nevertheless, actigraphy is helpful in determining the level of daytime and nighttime activity, especially for cancer patients who complain of fragmented nocturnal sleep.

## Therapeutic Approaches

### PHARMACOTHERAPY

Hypnotics, both benzodiazepines and non-benzodiazepines, are the class of medications most often prescribed. Benzodiazepines and their active metabolites vary in their half-life.<sup>5,74</sup> Those agents with longer half-lives are associated with residual effects, including disinhibition and daytime sedation, which lead to significant impairments in cognitive and psychomotor functioning.<sup>54</sup> Furthermore, rebound insomnia has been problematic in patients taking this class of medications for either chronic insomnia complaints or as an adjuvant to cancer treatments. This phenomenon can occur in all short- and intermediate-acting hypnotics. Rebound insomnia can be related to dosage and duration of treatment. However, as previously stated, benzodiazepines are the common first-line treatments for short-term insomnia, anxiety disorders, significant psychophysiological insomnia or childhood-onset insomnia, restless legs/period leg movements, pain, and any insomnia that is refractory to other treatments. A list of medications, including benzodiazepines, is shown in Table 7 along with their half-lives and typical dosages for the treatment of insomnia. Healthcare professionals generally use benzodiazepines as the first line of treatment for short-term insomnia due to its sedative effects.

**Table 8****Plan for Using Hypnotic Medications for Treatment of Insomnia****Drug Selection**

Consider pharmacokinetic properties

- Absorption
- Duration of action (half-life, dosage, chronicity)

**Behavioral Aspects**

Dictate a specific plan (dosage/timing)

- Forbid unsupervised dose escalation by patient; changes in dosage are made by physician only

Medication is taken before bedtime only

Outcome should be carefully monitored

- Evaluate compliance with treatment plan
- Evaluate changes in sleep duration and quality

Continue to explain importance of behavioral changes

- Monitor sleep habits to ensure they do not deteriorate
- Suggest additional changes as needed

Although cognitive behavioral treatment has established efficacy in treating both short-term and long-term insomnia, it is “time-invasive,” because many cancer patients want their sleep restored as soon as possible and do not want to wait several weeks for sleep improvement. Cognitive-behavioral treatment is highly recommended for long-term insomnia associated with psychological and/or behavioral components.

Nonbenzodiazepine hypnotics, such as zolpidem (Ambien) and zaleplon (Sonata), have shorter active metabolic half-lives and are therefore less frequently associated with daytime residual effects.<sup>75</sup> They also have a more specific and selective hypnotic mechanism of action than broader based medications and are thus less likely to be associated with side effects. However when these medications are prescribed inappropriately (eg, patient takes short-acting medication before bedtime for sleep maintenance difficulties) or when dose escalation and/or tolerance occur, these medications can worsen insomnia complaints. Pharmacotherapy for chronic insomnia is not recommended, except on a short-term basis and as an adjunctive treatment. The possibility of a primary sleep disorder should always be ruled out prior to pharmacologic treatment.

Additional nonbenzodiazepine medications (Table 4) commonly used for insomnia due to their sedating effects and low abuse and tolerance potential include but are not limited to the neuroleptic agents (eg, olanzapine [Zyprexa] and quetiapine [Seroquel]) and sedating antidepressant agents (eg, mirtazapine and amitriptyline). Over-the-counter hypnotic medications, including antihistamines, are not generally recommended because of the potential for abuse, tolerance, and unsupervised dose escalation.

Stepanski et al<sup>76</sup> suggest that once it is determined that a hypnotic medication should be part of the treatment plan, caregivers should follow a series of steps to most effectively choose a therapy (Table 8). Additionally, consider tapering and/or withdrawing medication once a sustained therapeutic point has been achieved. A general rule of thumb is to prescribe medica-



### Case History 3: Combined Approach to Treating Sleep Secondary to a Mood Disorder

Mrs. B, a 48-year-old married full-time homemaker, self-referred for sleep disturbance. On interview, she looked tired, worn, and was emotionally distressed. She reported being a good sleeper until she was diagnosed with chronic lymphatic leukemia. During this time, her husband filed for divorce. She spent many sleepless nights lying awake in bed trying to fall asleep while ruminating about her health, the divorce, and its implications for her two college-aged children. She reported moderate-to-severe depression but denied suicidal ideations. Mrs. B initially declined psychotherapy and antidepressant treatment because she wanted to “restore her sleep without psychotropic medication.” She was taking zolpidem (10 mg at bedtime) with no improvement in sleep duration or quality.

She was diagnosed with a sleep disorder secondary to a mood disorder. Treatment consisted of weekly review of sleep logs and stimulus control, sleep restriction, and cognitive-behavioral therapies. A “worry journal” was also included in this treatment regimen. She appeared very motivated in initiating treatment.

Review of 2 weeks of sleep logs revealed no difference in baseline functioning (sleep efficiency rating of 72%). Patient was adhering to the stimulus control and sleep restriction treatments, but her mood disturbance was severely impacting sleep functioning. At this point, Mrs. B agreed to attend psychotherapy but declined medication treatment. Review of another 2 weeks of sleep logs revealed a mild increase in sleep efficiency (74%) and sleep-quality ratings. After one month of treatment, patient agreed to antidepressant medication. She was prescribed sertraline (25 mg) and trazodone (50 mg at bedtime for its sedating effect) and within 3 weeks her sleep efficiency increased to 80% and sleep duration and quality improved. Within 6 weeks, patient was sleeping 8–9 hours per day and sleep efficiency improved to 90%. Antidepressant medication was discontinued after 1 year, and she remained free of psychiatric symptoms and sleep disturbance.

tions for short-term use (ie, no more than 3–4 weeks) and be aware of rebound insomnia following discontinuation.<sup>42</sup>

### BEHAVIORAL TREATMENT

Table 9 summarizes the three general approaches to behavioral treatment (sleep hygiene, stimulus control, and sleep restriction),<sup>26,77</sup> as well as common relaxation strategies used in managing insomnia. Mills and Graci<sup>2</sup> provide a more thorough review of behavioral and cognitive-behavioral treatment strategies. After a brief educational session, the patient initiates the behaviors at home. During subsequent clinic visits, a follow-up inquiry of the success of these behaviors is warranted, as is a discussion of specific barriers to achieving the goals of treatment. All three require that patients monitor their sleep patterns as they initiate these changes while monitoring their sleep/rest/wake times using a sleep self-monitoring form or other assessment instrument.

In addition to these three specific strategies, a more general cognitive-behavioral approach is implemented. For example,

**Table 9**

### Summary of Common Treatment Strategies for Insomnia

#### Sleep Hygiene

Sleep hygiene refers to the organization of activities to minimize sleep disturbance. Typically, it incorporates the following behaviors:

- Reducing the intake of nicotine, caffeine, and other stimulants.
- If stimulants must be taken, avoid them in the afternoon or evening.
- Avoid alcohol near bedtime.
- Keep a regular daytime schedule for work, rest, meals, treatment, exercise, and other daily activities.
- Exercise regularly, but only in the earlier part of the day rather than in the late afternoon or evening.

#### Stimulus Control

The overall goal of stimulus control is to train the patient, through a learning paradigm, to associate the bed with sleeping and sleeping with the bed. In addition, the patient learns to “set” his or her sleep/wake cycle. To achieve these goals, the following behaviors are suggested:

- Go to bed only when sleepy.
- No activity should be pursued in bed other than sleep (sexual activity is an exception); in other words, reading, eating, watching television, or completing homework is not to be done in bed but in another area of the home.
- If sleep does not come within 15 or 20 minutes of retiring at night, get out of bed and engage in relaxing behavior, returning to bed only when sleepy (this may be repeated as often as needed throughout the night).
- Wake at the same time every day, regardless of the amount of sleep achieved during the night.
- Avoid daytime naps.

#### Sleep Restriction

A sleep log is kept to determine baseline sleep times following the onset of sleep disturbances to determine sleep efficiency. In other words, if the patient spends 8 hours in bed but only achieves 4 hours of sleep, on average, his sleep efficiency is 4/8 or 50%. The patient is then directed to spend only 4 hours in bed each night. He does this until he achieves a sleep efficiency of 90% or more (3.6 hours). Then ½ hour is added to his allotted time in bed, and he maintains this sleep schedule until he again achieves a sleep efficiency of 90%. This pattern is followed until he reaches his target sleep time.

#### Progressive Muscle Relaxation

In this technique, the patient learns to stretch and relax successive areas of the body in an effort to “teach” the body what relaxation feels like.

#### Biofeedback

Biofeedback allows the patient to control body temperature and tension using an electronic feedback system. This technique requires both equipment and training and is not likely to be of benefit to patients who have multiple medical problems to address.

#### Guided Imagery

A patient is directed to sit or lie comfortably and take two or three deep breaths, closing his or her eyes. Imagery takes place in either the form of an audiocassette tape or guided by a nurse or clinician to a peaceful scene. The patient is encouraged to feel peaceful, relaxed, calm, satisfied, and without pain. Patients can learn to use these techniques at home before retiring for the evening.

Adapted from Mills and Graci<sup>2</sup>

many patients who have difficulty sleeping begin to worry about their lack of sleep and the nightly struggle to achieve restful sleep. They may ruminate more about their sleep patterns than the current psychosocial stressors they are experiencing. They begin to develop cognitions that only amplify the

#### Case History 4: Behavioral Treatment of a Substance-Induced Sleep Disorder

Ms. E is a 34-year-old, single woman employed at a postal service center. She was diagnosed with breast cancer and had a mastectomy followed by chemotherapy and radiation therapy. Cancer treatment ended 2 months ago. Her oncologist referred her for sleep maintenance difficulties. Patient denied any significant psychiatric history. She denied tobacco, caffeine, or recreational drug usage. The onset of Ms. E's sleep maintenance difficulties began when her oncologist prescribed venlafaxine for hot flashes. Ms. E discontinued venlafaxine and within 1 week her sleep disturbance subsided. Relaxation and guided imagery techniques were utilized for nighttime awakenings associated with nocturnal sweating. She utilized these techniques on nights when her hot flashes were problematic, which decreased time spent awake and increased sleep duration and sleep quality.

problem. Sleep difficulties may be seen as potential contributors to ongoing problems.

Such patients are likely to benefit from relaxation techniques. They range from relatively simple techniques that require 3–5 minutes of teaching to much more complex shifts in

the patients' view of life, which may require 2 months or more of teaching. Some of these techniques are progressive muscle relaxation, biofeedback, and guided imagery (Table 9).

#### Conclusion

The cause of chronic sleep difficulties is multifaceted, and until recently, little attention has been given to the pathogenesis of cancer-related insomnia. Educating patients and health professionals about sleep is important yet often overlooked. Clinicians need to inquire about the nature, duration, and severity of the insomnia complaint and determine how these factors contribute to the onset and maintenance of insomnia.

Cancer patients are often reluctant to raise the question of sleep with their physician or other healthcare providers.<sup>2,65</sup> Therefore, unless the nurse or physician directly inquires about sleep disturbance, the issue is likely to remain unaddressed. Nurses, physicians, and other healthcare providers are in a unique position to greatly improve the quality of sleep in cancer patients. The overarching objective of treating insomnia complaints is to improve daily functioning and increase quality-of-life ratings. Cancer patients face many challenges; sleep problems do not have to be one of them.

Peer viewpoints on this article by Drs. Josée Savard and Elizabeth Kvale appear on pages 361 and 365.

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