

# Cancer-Related Insomnia

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## Abstract

Insomnia increases cancer symptom burden and impairs quality of life. The lack of standard definitions and treatment guidelines makes management difficult. Insomnia is common in most cancers but appears particularly so in lung, breast, and head and neck tumors. Older women seem most susceptible. Insomnia not only affects patients with cancer but also caregivers and families. Systematic screening is important. Few validated assessment scales are available. Nonpharmacologic therapies like cognitive behavioral therapy may help. New nonbenzodiazepine hypnotics may have some therapeutic advantages over older agents. Management of associated or contributory symptoms like fatigue, pain, and hot flashes with appropriate symptom-specific agents is important. Successful management may have a significant positive impact on global quality of life.

## Keywords

cancer, insomnia, quality of life, symptoms, therapeutics

## Introduction

Sleep is a highly structured and well-organized activity with circadian periodicity. It is defined as a natural rhythmic state of rest for the mind and body.

Sleep is regulated by an interplay of internal biologic processes and environmental factors.<sup>1-3</sup> Quality sleep is important for mental and physical restoration and energy conservation.<sup>3</sup> It also helps thermoregulatory and immune processes.<sup>3</sup> Insomnia is a complex physiological disorder and can have both medical and nonmedical etiologies (Table 1). Sleep disturbances are associated with various common disease factors (Table 1), which include cardiovascular, musculoskeletal, and respiratory disorders.

Every sleep episode consists of 2 phases, nonrapid eye movement (NREM) and REM. The latter includes electroencephalographic activation, dreams, and muscle atony.<sup>1,3-5</sup> The NREM phase in contrast is characterized by decreased physiologic function but preserved muscle tone. It has 4 stages; stage 1 is the lightest and stage 4 is the deepest sleep. Stages 2 and 3 are known as delta (or slow wave) sleep.<sup>1,3-5</sup> Delta sleep predominates in the last third of the night.<sup>1,3-5</sup> From initial drowsiness before sleep onset, the individual first drops to stage 1, then progressively to stages 2, 3, and 4. This initial sequence is followed by a return from stage 4 to stage 2 and then the first REM sleep. The duration of REM phases increases throughout the night. The entire cycle lasts about 90 minutes and is repeated 4 to 5 times every night.

Insomnia (habitual sleeplessness) is a heterogeneous complaint that may involve difficulties falling asleep, trouble staying asleep (with prolonged nocturnal awakenings), early morning awakening (with inability to resume sleep), or a complaint of nonrestorative sleep.<sup>1</sup> Sleep disorders also include

many other problems characterized by insomnia, excessive daytime sleepiness or abnormal movements, and behaviors or sensations during sleep.<sup>5</sup> Typically, a patient or family member will provide a general report of difficulty sleeping. Further enquiry should then characterize the sleep disorder.

The International Classification of Sleep Disorders grouped the insomnias into 3 categories:

1. Dyssomnias: difficulty initiating or maintaining sleep or excessive sleepiness.
2. Parasomnias: abnormal behaviors or sensations during sleep.
3. Sleep disorders that accompany mental, neurologic, or other medical disorders.<sup>5,6</sup>

Sleep difficulties of any type are widely recognized among the general public to impair the quality and energy of daily life. Sleep deprivation has profound effects on mental function. Because of this, it has been employed as a (controversial) security interrogation technique. Fatigue and excess daytime sleepiness are the most common obvious consequences of sleep disorders in daily life.<sup>5</sup> Insomnia, when mild, may cause only small decrements in social and occupational function, but if

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**Table 1.** Cancer-Related Insomnia: Etiological Factors.

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|   |
|---|
| Predisposing  |
| <ul style="list-style-type: none"> <li>• Older age</li> <li>• Gender (females)</li> <li>• Family history</li> <li>• Personal history</li> <li>• Hyperarousability trait</li> <li>• Psychiatric disorder</li> </ul>  |
| Perpetuating  |
| <ul style="list-style-type: none"> <li>• Maladaptive sleep behaviors               <ul style="list-style-type: none"> <li>Excessive time in bed</li> <li>Irregular sleep-wake schedule</li> <li>Sleep interfering activities</li> </ul> </li> <li>• Faulty sleep attitudes               <ul style="list-style-type: none"> <li>Unrealistic sleep expectations</li> <li>Faulty sleep, appraisals</li> </ul> </li> </ul>   |
| Precipitating (cancer specific)   |
| <ul style="list-style-type: none"> <li>• Disease Factors:               <ul style="list-style-type: none"> <li>Tumors that increase corticosteroid production</li> <li>Symptoms from tumor invasion</li> </ul> </li> <li>• Treatment Factors:               <ul style="list-style-type: none"> <li>Surgery (aesthetic or functional impairment)</li> <li>Hospitalization</li> <li>Radiotherapy</li> <li>Chemotherapy</li> <li>Corticosteroids</li> <li>Hormonal fluctuations</li> </ul> </li> <li>• Medications</li> <li>• Concomitant cancer symptoms like pain, fatigue, delirium</li> <li>• Psychiatric disturbances</li> <li>• Stress from cancer/treatment</li> <li>• Bone marrow transplantation</li> </ul> |

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severe can be very debilitating, with multiple neuropsychological deficits that affect daytime function and quality of life.<sup>6</sup> Fortunately, many sleep problems can be effectively treated.<sup>2</sup>

Insomnia is a prominent cancer symptom yet has received little attention,<sup>1-4</sup> despite its adverse and diffuse impact on both physical and psychological function. Insufficient or poor quality sleep is the commonest<sup>5</sup> complaints in those with cancer-related insomnia (CRI). Cancer and related treatment of symptom impact quality of life; insomnia increases symptom burden and distress both directly and indirectly. Unmanaged cancer-related symptoms like insomnia can have significant effects on health care system costs due to increased hospitalizations and medical consultation.<sup>2</sup>

The paucity of literature on CRI and lack of assessment and management guidelines are therapeutic challenges. It is likely that better knowledge of the nature and prevalence of sleep problems among patients with cancer may stimulate new approaches to supportive care. The common general medical conditions associated with sleep disturbances are also frequent comorbidities in patients with cancer. Improved sleep function may also have biological benefits in cancer beyond routine daily psychological and physical function. In this clinical review, we discuss the physiological effects of insomnia in cancer and examine the available evidence-based management data to assist therapy.

## Insomnia in Cancer

### *Cancer Insomnia: Isolated Complaint or Symptom Cluster?*

In cancer, insomnia may be perceived as an isolated complaint or identified as part of a symptom cluster. Sleep disturbances have been identified in various neuropsychologic and other cancer symptom clusters. In particular, insomnia is believed to coexist with pain and fatigue and psychiatric conditions like anxiety, depression, and various mood disorders.<sup>7</sup> Insomnia has not gained as much attention as other equally frequent cancer symptoms, even though it may belong to some highly prevalent symptom clusters. Awareness of the symptom cluster concept may help identify these symptom associations with CRI and stimulate appropriate targeted assessment and management.

### *Insomnia and Cancer Fatigue*

In cancer, insomnia is often contemporaneous with other common symptoms, but the relationship with fatigue deserves special attention. Fatigue can be a cause and/or consequence of insomnia. The pathophysiology of cancer-related fatigue (CRF) may be central in origin and can itself also be a distressing problem. The CRF can be a part of a vicious circle, where if one symptom is not addressed both worsen. Recognition of the association between CRF and CRI should help design appropriate interventions and also minimize any adverse effects of therapy.

### *Is CRI Different?*

Cancer-related insomnia has not been defined as a separate entity. As assessment and management is little studied, it is currently impossible to differentiate it from other types or causes of insomnia. Intuitively, it likely differs in etiology and associated factors, given the complex psychological and physical ramifications of metastatic cancer. To approach CRI as a defined symptom or symptom complex would likely improve diagnosis and management, given the major challenges in symptom control in advanced cancer.

### *Pathophysiology of CRI*

Pathophysiology is unknown. There are multiple factors possibly present in the patient with cancer that can disturb sleep. Insomnia (like pain) can thus be considered to be due to the cancer itself, a consequence of other cancer symptoms and/or related to cancer treatment. Some potential precipitating physical factors are evident. The general tumor mechanisms that disrupt body function include pressure, obstruction, invasion of sensitive structures, tissue destruction, and inflammation.<sup>8</sup> Primary or metastatic brain tumors may disrupt neurohormonal sleep regulation and brain wave patterns through all sleep stages. Tumor growth in the upper or lower respiratory system and the muscle weakness of advanced disease may lead to shortness of breath, sleep apnea, hypoxia, or hypercapnea. These may disrupt the sleep regulatory mechanism and cause arousal.<sup>5,8</sup> Cancer may

**Table 2.** Cancer-Related Insomnia: Common Drugs.

- Antidepressants: SSRIs
- Antiemetics: prochlorperazine, metoclopramide, granisetron
- Chemotherapy
- Corticosteroids: dexamethasone
- Diet supplements: caffeine
- Hormonal therapy: tamoxifen, leuprolide
- Neuroleptics: methyphenidate
- Opioids: ataxic breathing with central apnea
- OTC drugs: aspirin
- Sedatives and hypnotics
- Sympathomimetics: albuterol
- OTC drugs: aspirin
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Abbreviations: OTC, over-the-counter; SSRIs, selective serotonin reuptake inhibitors.

also alter various hormone levels and secondarily interfere with sleep homeostasis.<sup>8</sup> Cytokines like interleukins, interferons, and tumor necrosis factor (released due to tumor growth) can activate the hypothalamic–pituitary–adrenal axis to release corticosteroids, including cortisol,<sup>8</sup> which in turn may interfere with normal sleep. In advanced cancer, people may be at higher risk for disrupted circadian function.<sup>8</sup> One clinical study reported flattened rest activity circadian rhythm in metastatic colon cancer.<sup>8</sup> Malignant tumors, particularly those of the respiratory and central nervous systems, may severely affect sleep processes.<sup>9</sup> Screening for obstructive sleep apnea and appropriate management may help insomnia in head and neck cancer.

Disease-specific factors probably also play a role in CRI. Etiologic factors (Table 1) prevalent in cancer include:

1. predisposing factors;
2. precipitating factors;
3. perpetuating factors.

Some likely precipitating factors are cancer specific, whereas others may affect anyone in the general but otherwise healthy population. Important nonmodifiable factors include age and gender, personal history of sleep problems, underlying psychiatric disorders, and a diagnosis of advanced cancer.<sup>8</sup>

Insomnia can occur anytime during the cancer process: at initial diagnosis, the time of surgery, during antitumor treatment, at recurrence, and during the palliative and terminal stages. Pain can affect both sleep initiation and maintenance.<sup>7</sup> Sleep disturbances are also a typical clinical feature of delirium. Many commonly prescribed drugs may cause insomnia (Table 2). As most malignancies occur in older population with frequent comorbidities, other drugs like antihypertensives, nonprescribed, and over-the-counter agents like caffeine and nicotine can also cause insomnia.

### Prevalence of Cancer Insomnia

The prevalence varies from 19% to 63% due to imprecise definitions and measurement.<sup>3,4,7</sup> One study identified sleep

difficulties in 40% of the patients with cancer compared to 15% of the controls.<sup>10</sup> A survey of 100 palliative medicine patients reported that 72% experienced complex sleep disturbances.<sup>10</sup> These included not feeling rested in the morning (72%) and difficulty staying awake (63%) or falling asleep (40%).<sup>11</sup> A prevalence study in 1635 patients with cancer reported insomnia as the most frequent single symptom in 59%.<sup>11</sup> One large study reported insomnia in 31% of the patients.<sup>2</sup> It commonly involved multiple awakenings (76%) and occurred around the time of cancer diagnosis (48%).<sup>2</sup> Single most commonly reported sleep disruption in some studies was frequent waking.<sup>1,2</sup> Older people and women seem more likely to report cancer-related insomnia.<sup>1,3,7</sup>

Irrespective of the type of tumor, cancer-related insomnia was evident in 45% of the patients with cancer who underwent surgery, 39% of patients who underwent radiation therapy, and 35% of patients who underwent chemotherapy.<sup>2,12</sup> This study noted that of 300 patients with insomnia, 76% had maintenance insomnia (with several awakenings during the night) and 44% had difficulty falling asleep.<sup>2,12</sup> In the same study, commonly identified reasons for insomnia included pain or discomfort, concerns about family and finances, and physical effects of the cancer.<sup>2</sup> Lung and breast cancers may have one of the highest incidences of insomnia.<sup>2,7</sup> People with lung cancer seem more likely to take sleep medications (40%) and experience restless legs (47%) compared to other cancers.<sup>2,12</sup> Little research has been done on the insomnia of advanced disease. In one study in advanced pancreatic cancer, the predominant symptom was pain (82%), but 54% had sleep problems.<sup>13</sup>

Table 3 illustrates prevalence and characteristics of CRI.<sup>2,13-26</sup>

### Impact of CRI

Cancer-related insomnia has a negative impact on quality of life.<sup>4,27</sup> Physical, psychological, social, and existential suffering is exaggerated by sleep deprivation.<sup>28</sup> Sleeplessness diminishes coping capacity, exacerbates pain and discomfort, and increases the perceived severity of illness.<sup>4</sup> Insomnia in patients with cancer also affects caregivers and families both directly and indirectly.<sup>29</sup> There is little information on family/caregivers sleep problems and their quality of life. Family caregivers of loved ones with advanced cancer also often reported sleep disturbance but were reluctant to take hypnotics.<sup>30</sup>

The effects of insomnia in patients with cancer can be divided into 2 broad categories (Table 4):

1. physiological;
2. psychological.

Insomnia often coexists with neuropsychological conditions like anxiety and depression. Although they can cause insomnia, they may also be consequential. The interrelationships between these symptoms accordingly appear complex and are poorly understood. Longitudinal studies suggest that people with persistent insomnia are at higher risk for subsequent depression, anxiety, and substance abuse.<sup>31,32</sup>

**Table 3.** Prevalence and Characteristics of Cancer Insomnia.

| Cancer                                      | Prevalence and features  |
|---|--|
| Breast <sup>14,15,16</sup>                  | <ul style="list-style-type: none"> <li>– 48% sleep problems; 28% used sleep medication</li> <li>– 50% disturbed sleep from voiding</li> <li>– 40% sleep hypnotic</li> <li>– 68% on tamoxifen had insomnia from menopausal symptoms</li> <li>– Significantly poorer sleep in breast cancer compared to benign breast tumors</li> </ul>  |
| Lung <sup>2,17,18</sup>                     | <ul style="list-style-type: none"> <li>– More awakenings and longer wake times, more day naps</li> <li>– 34% sleep disturbance, 47% restless legs, 40% hypnotics</li> <li>– 52% insomnia on radiotherapy or chemotherapy</li> <li>– Twice as long to sleep compared to breast cancer</li> <li>– Early morning awakenings, excessive daytime sleepiness and prolonged wake periods</li> </ul> |
| Prostate <sup>2,19</sup>                    | <ul style="list-style-type: none"> <li>– 18% insomnia 15% sleep medication</li> <li>– Most prevalent were overly fatigued (40%), feeling very sleepy (30%), restless legs (37%)</li> <li>– Sleep maintenance main problem</li> <li>– Primary reason include bladder irritation, frequent voiding, and hot flashes</li> </ul>   |
| Head and Neck <sup>20,21</sup>              | <ul style="list-style-type: none"> <li>– Seventh most prevalent symptom</li> <li>– 41% insomnia; 78% reported it distressful</li> </ul>  |
| Gynecological <sup>22</sup>                 | <ul style="list-style-type: none"> <li>– Excessive sleepiness, especially during radiation therapy</li> <li>– 30% sleep problems, increased to 68% with treatment</li> <li>– Difficulty falling asleep and frequent awakenings</li> </ul>  |
| Gastrointestinal <sup>2</sup>               | <ul style="list-style-type: none"> <li>– Lowest prevalence (7%)</li> <li>– 20% sleep medication</li> </ul>   |
| Skin <sup>23</sup>                          | <ul style="list-style-type: none"> <li>– Melanoma patients reported daytime fatigue, difficulty morning waking, and not feeling rested</li> <li>– Women reported more sleep problems and lower sleep quality than men</li> </ul>   |
| Hematological Malignancies <sup>24,25</sup> | <ul style="list-style-type: none"> <li>– Most common in leukemia and lymphoma were waking during the night (77%), not feeling rested (60), and waking up too early (59%)</li> <li>– Difficulty sleeping a significant predictor of tiredness for chemotherapy patients</li> </ul>  |
| Advanced Cancer <sup>26,27</sup>            | <ul style="list-style-type: none"> <li>– 54% Sleep problems</li> <li>– 47% Prevalence</li> </ul>   |

**Table 4.** Cancer-Related Insomnia: Impact.

| Physiological  | Psychological  |
|--|--|
| <ul style="list-style-type: none"> <li>● Health problems (nonspecific pain, headaches, malaise)</li> <li>● Increased medical consultations and hospitalizations</li> <li>● Higher mortality—from insomnia and/or chronic hypnotic abuse</li> <li>● Immunosuppression (decreased natural killer T-cell activity and lower concentration of helper T cells)</li> </ul> | <ul style="list-style-type: none"> <li>● Impaired cognitive and psychomotor skills</li> <li>● Fatigue</li> <li>● Decreased daytime function</li> <li>● Secondary anxiety, depression, mood disorders</li> <li>● Risk of substance abuse</li> <li>● Heightens suffering</li> <li>● Family Distress</li> </ul> |

People with insomnia reported more health problems, medical consultations, and hospitalizations compared to those who are good sleepers.<sup>33,34</sup> Studies have suggested insomnia has an immunosuppressive effect but are inconclusive. Total sleep duration, sleep efficiency, and non-REM sleep duration have been positively correlated with natural killer cell activity.<sup>1</sup> A satisfactory amount of sleep has also been associated with more circulating helper T cells.<sup>1</sup> Insomnia might therefore impact the

natural history of a tumor by interfering with the immune response to a cancer.<sup>1</sup>

### Assessment of CRI

Assessment scales for common symptoms often used in both early and advanced cancer (like the Edmonton Symptom Assessment Scale) do not include insomnia. This is surprising,

**Table 5.** Cancer-Related Insomnia: Sleep Hygiene.

- Think positive
- Fixed bed and wake times
- No daytime naps
- No exercise immediately before sleep
- Minimize fluids before bedtime
- Avoid late caffeine, alcohol, nicotine, food
- Bedtime ritual to relax (warm bath, read)
- Comfortable sleep environment (minimize noise, light, and extreme temperatures)
- Simple relaxation techniques
- Avoid clock watching
- 20-minute “toss and turn” rule—get up if no sleep onset within this time

**Table 6.** Cancer-Related Insomnia: Treatment Barriers.

|               |   |
|---------------|---|
| Health system | <ul style="list-style-type: none"> <li>• Lack of standard guidelines</li> <li>• Lack of resources for patients and physicians</li> <li>• Inadequate assessment methods</li> </ul>                           |
| Physician     | <ul style="list-style-type: none"> <li>• Lack of knowledge about physiological impact</li> <li>• Insufficient education in symptom control</li> <li>• Focus on antitumor treatment</li> </ul>               |
| Patient       | <ul style="list-style-type: none"> <li>• Inability to report</li> <li>• Minor compared to a cancer diagnosis</li> <li>• Belief physicians cannot help</li> <li>• Fear of medication side effects</li> </ul> |

given the prevalence and potential impact on quality of life. Many patients with cancer do not appear to report their sleep problems: 80% assume it is from their treatment, 60% (wrongly) believe it is temporary, and almost 50% feel that their physicians cannot help.<sup>35-37</sup>

Like other cancer symptoms, recognition is the key to effective management. It is important to screen everyone by a simple clinical question such as “How are you sleeping?” Assessment should then extend beyond that, with specific enquiry about different sleep disturbance components.<sup>9,38</sup> Various approaches are recommended in figure 1.

Text Box: Cancer-Related Insomnia: Diagnostic Criteria.<sup>1</sup>

|  |
|--|
| Occurs at least 3 nights per week                                |
| Delayed sleep onset (>30 minutes to initiate sleep)              |
| Difficulty with sleep maintenance (>30 minutes nocturnal waking) |
| Causes significant impairment in daytime function                |

It is important to characterize the sleep pattern and whether the sleep pattern changed with cancer diagnosis, treatment, or hospitalization.<sup>3</sup> Questionnaires may help but unfortunately no single assessment scale is superior. The Pittsburgh Sleep Quality Index is commonly used. It is a 19-item self-rated inventory of symptoms of sleep disturbance, with higher scores for worse sleep quality.<sup>39</sup> It may be difficult to administer in

clinical practice. Others like The General Sleep Disturbance Scale or the Clinical Sleep Assessment Scale are less popular.<sup>40</sup> The self-rated Zung Depression Scale has poor sensitivity and specificity for insomnia.

Sleep diaries can be used as subjective measures. The burden of daily records may decrease reliability and have limited feasibility and consequent problems with missing data—especially in patients with cancer.<sup>40,41</sup> The insomnia severity index has been validated for screening in both cancer research and clinical practice.<sup>42</sup> The Clinical Sleep Assessment for adults was validated as a brief sleep disturbance assessment but needs additional investigation.<sup>43</sup>

Objective sleep measurement is done with polysomnography (PSG) and actigraphy. The PSG is the gold standard for detection of specific sleep and wake states.<sup>44</sup> It is usually performed in an overnight sleep laboratory and includes neurological and neuromuscular measurements (electroencephalogram, electrooculography, and electromyography) and assessment of cardiac and respiratory function. Ambulatory PSG can gather information in a natural environment. Wrist actigraphy is a measure that records movement over time and counts activity as an indirect measure.<sup>45</sup> The advantage is that data are collected in the natural environment. Actigraphy measurements correlate about 90% with PSG. None of the objective measures (PSG, Actigraphy) correlate well with subjective ones.<sup>46,47</sup> Given the current state of knowledge, a combination of subjective and objective measures are probably the best.

## Management of CRI

Cancer-related insomnia has a complex pathophysiology. Treatment should therefore be multimodal to include both non-pharmacologic and pharmacologic approaches. Before specific pharmacological treatment is considered, the emphasis should be to identify and manage precipitants and promote good sleep hygiene (Table 5). Barriers to effective intervention should be identified and eliminated where possible (Table 6).

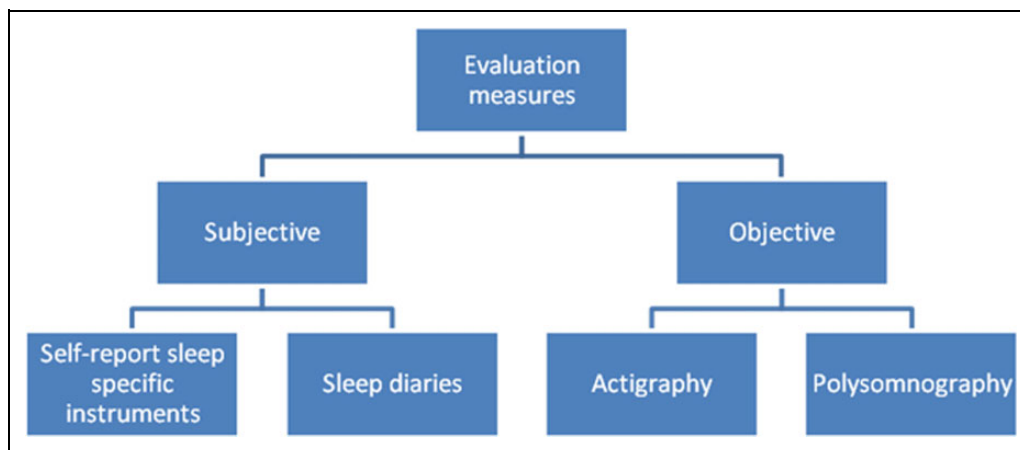
### Nonpharmacologic Therapy

Nonpharmacologic therapies have true long-term efficacy and importantly lack adverse effects and drug interactions.<sup>4</sup> Sleep improvement from psychologic management may be well maintained for up to 24 months after initial treatment.<sup>48</sup> Studies have demonstrated significant improvement in CRI with non-pharmacologic therapy. Stimulus control, daytime sleep restriction, and combined approaches are the most effective. Sleep hygiene education alone may produce only modest gains.<sup>49</sup>

Stimulus control therapy, relaxation training, and strategies aimed at consolidation of sleep and reduction of cognitive arousal improve sleep and lessen daytime fatigue with enhanced ability to perform activities.<sup>50</sup> One study reported improved sleep latency, efficiency, quality, duration, and daytime function from combined sleep hygiene, relaxation, and cognitive components.<sup>51</sup> When sleep hygiene and combined

**Table 7.** Cancer-Related Insomnia: Management.

| Nonpharmacologic   | Pharmacologic  |
|--|--|
| <ul style="list-style-type: none"> <li>• Relaxation therapy</li> <li>• Sleep restriction</li> <li>• Stimulus control</li> <li>• Cognitive/behavioral modification (biofeedback, guided imagery)</li> <li>• Sleep education</li> <li>• Combined approaches</li> </ul> | <ul style="list-style-type: none"> <li>• Benzodiazepine hypnotics</li> <li>• Nonbenzodiazepine hypnotics</li> <li>• Antidepressants</li> <li>• Antihistamines</li> <li>• Melatonin</li> <li>• Alternative treatments—kava kava, valerian root</li> <li>• Miscellaneous—treatment of cough, fatigue, hot flashes, pain, and so on.</li> </ul> |

**Figure 1.** Insomnia evaluation and assessment.

approaches were compared, the combined approach group had greater subjective sleep improvement but both showed similar objective improvements in sleep initiation, maintenance, and total sleep time and quality.<sup>52</sup> There is therefore empirical support for the efficacy of psychological behavioral therapies in CRI. In advanced disease, their role can be limited by severity of illness and undue patient burden.<sup>4</sup>

### Pharmacologic Management

In cancer, judicious use of hypnotic agents is appropriate supportive care, since they can significantly improve quality of life.<sup>3</sup> There is limited data about efficacy of hypnotic drugs in patients with cancer. Based on the abundant literature about pharmacologic agents in primary insomnia, there is therapeutic potential in cancer (Table 7). One concern is drug–drug interactions given the polypharmacy inevitable in metastatic cancer. Non-BZD hypnotic agents like zolpidem and escopiclone are said to have more receptor selectivity and fewer side effects.<sup>1</sup> Although there are few long-term studies on the tolerance, dependence, and safety of these agents, they are said to be superior to BZDs. Nevertheless, the therapeutic index of these agents in CRI has not received sufficient scrutiny to make any definitive statements about their relative merits.

Benzodiazepines are commonly used in clinical practice and decrease time to sleep onset, improve sleep efficiency, and impart a sense of restful sleep.<sup>53</sup> The drug onset and duration

of action should be the primary indicators to select the best one. Pharmacodynamic BZD interactions with opioids appear common with delirium, falls, and excess neuropsychological side effects. Long-acting BZDs may produce daytime drowsiness, dizziness, and cognitive impairments. Short-duration BZDs may be associated with tolerance, dependence, rebound insomnia, and daytime anxiety.<sup>1,3,4</sup> Short-acting BZDs are best used for sleep onset difficulty and intermediate BZDs for both sleep onset and maintenance problems. The traditional recommended approach is to use short-acting BZDs/non-BZD hypnotics for a short period of time (<4weeks). In practice, short-term use of hypnotic agents appears uncommon; once people use an effective hypnotic, most are reluctant to stop or change.

**Antidepressants.** Commonly used antidepressants for insomnia include amitriptyline, doxepin, mirtazapine, and trazadone. Although inexpensive and with little abuse potential, they should be used judiciously and in low doses in patients with cancer due to limited efficacy and significant side effects.<sup>54-56</sup> These include dry mouth, delirium, and postural hypotension. In addition, there are also pharmacodynamic interactions with opioids. Patients with cancer with both depression and insomnia nevertheless may benefit. Tricyclic antidepressants may have particular utility for those who also have neuropathic pain or headache with insomnia.<sup>4</sup> Trazadone in low doses can relieve insomnia, but data are limited on efficacy and tolerance. Mirtazapine can be used for insomnia associated with anorexia

and depression.<sup>57,58</sup> Both trazodone and mirtazepine can cause dry mouth and significant neuropsychological side effects, particularly in the frail and elderly individuals.

**Antihistamines.** There is no role for any antihistamine (such as diphenhydramine or hydroxyzine) in CRI. Patients develop tolerance to their sedative actions, and their side effects like dry mouth are burdensome,<sup>56,59</sup> particularly when used along with opioids. Again, excess neuropsychological side effects seem common.

**Melatonin.** Melatonin likely promotes sleep by regulation of the sleep–wake cycle.<sup>56,60,61</sup> It may help primary insomnia, but a role in CRI has not been studied. Dry mouth and constipation are common side effects. The melatonin receptor agonist, ramelteon, has a short half-life and though recommended for sleep onset problems<sup>62</sup> has not been studied in CRI.

**Alternative Treatments.** Agents like valerian root and kava kava have been promoted as natural treatments, but there is limited evidence to support their use.<sup>4,63</sup>

**Miscellaneous Agents.** Selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors that are used to treat hot flashes in breast cancer can also help in treating insomnia. Venlafaxine is most promising.

## Research in CRI

The available literature indicates a high prevalence of cancer-related sleep disturbances and a major impact on patients and the health care system. Several randomized controlled trials support cognitive behavioral therapy to improve sleep quality. Most of these had sleep as a secondary outcome, used controversial methodology, and studied predominantly breast cancer. More resources are required to focus on this common high-impact disorder. Future research should focus on the associations of insomnia with other symptoms, conceptual models to identify effective behavioral and pharmacological therapies, and clinically efficient assessment methods. Large trials in various cancers to identify well-tolerated effective hypnotics should follow.

## Summary

Cancer-related insomnia adds to cancer symptom burden and has a severe impact on quality of life. Despite being one of the commonest and most distressing cancer symptoms, it has been largely ignored by clinicians and researchers. Insomnia is common in most cancers, but particularly prevalent in lung, breast, and head and neck cancers. Lack of standard definitions and guidelines makes management difficult. Symptom clusters that include insomnia should be identified. Insomnia is well known to be associated with fatigue, pain, depression, and anxiety.

Older people and women may be more susceptible. Insomnia gets worse as cancer progresses. Insomnia not only affects patient's quality of life but also that of caregivers and families.

Undertreatment likely has significant impact on costs and health care system utilization due to its diffuse impact and consequently increased medical visits and hospitalizations.

Systematic screening for CRI is essential. Few validated scales are available. Although there is extensive literature on the pharmacologic and nonpharmacologic treatment of primary insomnia, there is little about CRI. Nonpharmacologic therapies like cognitive behavioral therapy have promising results, but more information is required. The role of pharmacotherapy for CRI is even more unclear. New-generation non-BZD hypnotics may offer some benefits. Management of important associated symptoms like fatigue, pain, and hot flashes with appropriate agents is important as part of a comprehensive therapeutic strategy.

## Authors' Note

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