

CONTINUING EDUCATION

Sleep-Wake Disturbances in People With Cancer Part I: An Overview of Sleep, Sleep Regulation, and Effects of Disease and Treatment

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Purpose/Objectives: To provide an overview of normal sleep, describe common sleep disorders, and discuss underlying sleep regulatory processes and how cancer, cancer treatment, and associated patient responses may adversely affect sleep.

Data Sources: Published peer-reviewed articles and textbooks.

Data Synthesis: The duration, structure, and timing of sleep have a profound impact on health, well-being, and performance. Patients with cancer may be at risk for disturbances in sleeping and waking resulting from disease- and nondisease-related circumstances that interfere with normal sleep regulation, including demographic, lifestyle, psychological, and disease- and treatment-related factors.

Conclusions: Patients with cancer are at high risk for sleep-wake disturbances.

Implications for Nursing: An understanding of normal sleep, sleep pathology, and the factors that can precipitate sleep disturbance provides a context for nurses to interpret sleep complaints in their patients, evaluate responses to sleep-promoting interventions, and guide decision making regarding referrals.

Key Points . . .

- ▶ The normal sleep-wake cycle is controlled by internal and external factors.
- ▶ Sleep disorders include an array of problems that are characterized by insomnia, excessive daytime sleepiness, or abnormal movements, behaviors, or sensations during sleep.
- ▶ A complete assessment of sleep examines nocturnal and daytime sleep-wake patterns.
- ▶ Patients with cancer experience complex and interacting factors that can adversely affect sleep-wake patterns.

In December 2001, the Oncology Nursing Society (ONS) held a retreat for advanced practice nurses to develop strategic plans to address critical issues in advanced oncology nursing practice. The members of the Evidence-Based Practice

Goal for CE Enrollees:

To enhance nurses' knowledge about factors that influence sleep in people with cancer.

Objectives for CE Enrollees:

- On completion of this CE, the participant will be able to
1. Describe the normal sleep-wake cycle.
 2. Describe how cancer and cancer treatment can affect sleep patterns.
 3. Outline the clinical implications of current evidence about interventions for sleep-wake disturbances in people with cancer.
 4. Identify needs for further research related to sleep disturbances in people with cancer.



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Work Group identified sleep-wake disturbances as problems commonly seen in practice for which clinicians lacked specific practice guidelines. Therefore, in consultation with ONS National staff and evidence-based practice experts, the group developed a work plan based on the processes described in the ONS Evidence-Based Practice Resource Center (ONS, n.d.) to synthesize evidence about sleep-wake disturbances in people with cancer. A team composed of clinicians, educators, and researchers implemented the work plan over a 12-month period. This article and its companion, "Sleep-Wake Disturbances in People With Cancer Part II: Evaluating the Evidence for Clinical Decision Making" (see p. 747), are the results of the work of this group. Part I provides background information necessary for clinicians to understand usual patterns of sleep and common sleep disorders. In addition, a theoretical model of sleep regulation will be presented along with a brief description of how cancer, cancer-related treatments, and associated patient responses may affect sleep regulatory processes. Part II will present a critical synthesis of the literature on sleep-wake disturbances in people with cancer and discuss the implications of the synthesis for oncology clinicians, educators, and researchers.

Introduction

Much remains to be discovered regarding the nature and purpose of sleep, but modern studies have revealed some of the secrets of this universal phenomenon. Although once believed to be a passive state, sleep now is known to be an active process regulated by multiple behavioral, neuroendocrine, and central nervous system factors. Insufficient or poor quality sleep has been shown to have a variety of adverse effects on important clinical outcomes. Eighty-eight primary sleep disorders have been recognized or proposed, and the field of sleep medicine has become a legitimate empirical subspecialty (Aldrich, 1999). Unfortunately, the dissemination of sleep-related information to healthcare professionals has not kept pace with scientific developments made in the field. In fact, as recently as the 1990s, the curricula of most medical and nursing schools had little or no didactic content on sleep (Rosen & Zozula, 2000). Therefore, not surprisingly, the sleep problems of patients frequently go unrecognized and untreated (Dement, 2000). In addition, many patients fail to discuss sleep problems with healthcare providers because their concerns have been dismissed previously or have never been evaluated. Similarly, although oncology nurses are aware that sleep problems are common, one study revealed that a significant number of patients never mentioned these problems and when they did, interventions were not offered (Engstrom, Strohl, Rose, Lewandowski, & Stefanek, 1999). To improve clinical outcomes, nurses need to understand and appropriately respond to the sleep problems experienced by patients with cancer.

Overview of Normal Sleep

The Function of Sleep

The function of sleep remains a topic surrounded by controversy. Some have postulated that sleep is important for mental and physical restoration and energy conservation, whereas others believe that sleep is primarily important for brain function (Aldrich, 1999; Zepelin, 2000). Sleep deprivation studies

have revealed that the most notable response to prolonged sleep loss is overwhelming sleepiness, suggesting that sleep fulfills essential needs. A meta-analysis of sleep deprivation studies demonstrated that total and partial sleep loss impair well-being and functioning, with mood followed by cognitive and motor performance being the most strongly affected (Pilcher & Huffcutt, 1996).

Sleep appears to play an important role in thermoregulatory and immune processes (Horne & Reid, 1985; McGinty & Szymusiak, 1990). Specific areas in the hypothalamus and basal forebrain integrate temperature and sleep control through a network of complex, interactive processes. For example, changes in brain temperature increase sleep depth, and deep sleep increases heat loss by stimulating vasodilation and reducing metabolic rate. Peripheral signals from skin thermosensors to these regions of the brain also can have a significant effect on sleep-wake states (Van Someren, 2000). In fact, the vasodilation of blood vessels in the feet in response to local warmth is an independent predictor of sleep onset (Krauchi, Cajochen, Werth, & Wirz-Justice, 1999). Many immune factors such as interleukin- (IL-) 1, IL-2, and tumor necrosis factor- α (TNF- α) have been shown to promote deep sleep, possibly because of associated fever and heat production (Dinarello & Bunn, 1997; Krueger & Fang, 2000). Thus, the interaction of sleep, thermoregulation, and immunologic responses may explain why patients become sleepy when they have fevers and infections (Krueger & Majde, 1994). Sleep deprivation also has been associated with a reduction in the activity of natural killer cells in response to a bacterial or viral load, suggesting a direct link between sleep and immune function (Benca & Quintans, 1997).

Sleep Stages and Cycles

The nocturnal sleep period consists of several stages and cycles that collectively are referred to as "sleep architecture." The structure and timing of the sleep stages and cycles can be studied objectively using polysomnography. These studies have demonstrated that two major types of sleep exist: rapid eye movement (REM) sleep and non-REM (NREM) sleep. NREM sleep is divided into four stages representing a relative continuum of depth; stage 1 is the lightest level of sleep, and stage 4 is the deepest. Stages 3 and 4 are referred to collectively as deep, delta, or slow wave sleep. In NREM sleep, electroencephalogram (EEG) activity becomes increasingly slower and mental activity becomes fragmented, but voluntary muscle control and tone remain intact. Thus, a common definition of NREM sleep is "a relatively inactive . . . brain in a movable body" (Carskadon & Dement, 2000, p. 15). In contrast, REM sleep is characterized by an increase in the irregularity of EEG activity (resembling wakefulness), bursts of REM, dreaming, and autonomic variability (e.g., increase in heart rate, respiration, blood pressure, and cerebral blood flow; decrease in temperature regulation). Complete paralysis of the voluntary muscles occurs because of accompanied hyperpolarization of the brain stem and spinal motor neurons (believed to occur so that people do not "act out" dreams). Therefore, a short, but useful definition of REM sleep is "a highly activated brain in a paralyzed body" (Carskadon & Dement, p. 16).

A typical night of sleep for a young adult consists of four to six cycles of NREM and REM sleep (see Figure 1). From an initial stage of drowsiness, an individual enters stage 1 NREM

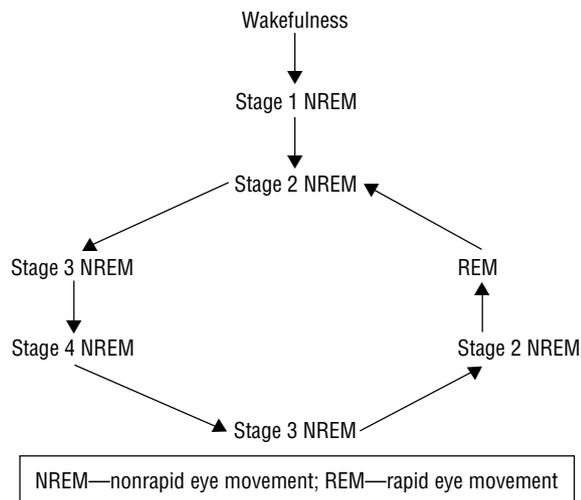


Figure 1. The Sleep Cycle

sleep and progresses to stage 4. This initial sequence is followed by a return from stage 4 to stage 3 and stage 2, leading into the first REM episode. NREM and REM sleep continue to alternate through the night in cyclical fashion with each cycle generally lasting about 90–110 minutes. Stage 1 sleep represents 2%–5% of total sleep, stage 2 represents 45%–55%, and stages 3 and 4 represent 13%–23%. Slow wave sleep predominates in the first third of the night, whereas REM sleep, which accounts for 20%–25% of total sleep, predominates in the last third of the night (Carskadon & Dement, 2000).

As humans age, variability in sleep architecture and sleep-wake patterns increases, making a typical night of sleep for older adults more difficult to describe (Williams, Karacan, & Hirsch, 1974). However, in general, published data indicate that, relative to younger people, older people spend more time in bed but less time asleep largely as a result of difficulty maintaining sleep and early morning awakening (Foley et al., 1995; Ganguli, Reynolds, & Gilby, 1996). Older adults also have more stage 1 sleep and less stage 2, 3, and 4 sleep (Buysse et al., 1992; Hirshkowitz, Moore, Hamilton, Rando, & Karacan, 1992; Hoch et al., 1994; McCall, Erwin, Edinger, Krystal, & Marsh, 1992). Although time spent in REM sleep has a tendency to shorten, the proportion of REM sleep to total sleep remains relatively unchanged into healthy old age (Carskadon & Dement, 2000).

Measurement of Sleep

The gold standard for the objective measurement of sleep is polysomnography, the simultaneous recording of multiple physiologic variables, including EEG, electromyogram, and the electrooculogram (Carskadon & Rechtschaffen, 2000). The electrocardiogram, respiratory patterns, and blood oxygen levels using pulse oximetry also are measured frequently. Although typically performed in a sleep laboratory, ambulatory polysomnography recorders provide an alternative for the objective measurement of sleep in home settings (Edinger, Erwin, Fins, Marsh, & Krystal, 1995; McCall et al., 1992). Specific measures of sleep that are obtained from polysomnography include sleep latency or the time taken to fall asleep, latency to various sleep stages, the percentage of time in each stage, total sleep time, sleep efficiency or the time spent sleeping while in

bed, the number of arousals or awakenings that occur throughout the night, and other events such as apneas and limb movements (Carskadon & Rechtschaffen) (see Figure 2).

Actigraphy, an alternative method used to measure sleep objectively, relies on monitoring periods of activity and rest (Ancoli-Israel, 2000). Using a battery-operated wristwatch-sized microprocessor that senses movement with a piezoelectric beam, continuous motion data can be obtained for long periods. Computer algorithms allow for analysis of activity and nonactivity as well as scoring of sleep and wakefulness. Actigraphy cannot determine sleep stages, but information on total sleep time, percent of time spent awake, number of awakenings, time between awakenings, and sleep latency can be obtained (American Sleep Disorders Association, 1995). Actigraphy data correlate well with polysomnography data, particularly when sleep is normal (Cole, Kripke, Gruen,

Actigraphy: a biomedical instrument used to measure body movement

Apnea: cessation of airflow at the nostrils and mouth lasting at least 10 seconds; the three types of apnea are obstructive, central, and mixed. Obstructive apnea is secondary to upper-airway obstruction, central apnea is associated with a cessation of all respiratory movements, and mixed apnea has both central and obstructive components.

Arousal: an abrupt change (i.e., over 3–14 seconds) from a deeper stage of nonrapid eye movement sleep to a lighter stage or from rapid eye movement sleep to wakefulness

Circadian rhythm: an innate daily fluctuation of physiologic or behavior functions, including sleep-wake states, generally tied to the 24-hour daily light-dark cycle; this rhythm sometimes occurs at a measurably different periodicity (e.g., 23 or 25 hours) when light-dark and other time cues are removed.

Deep sleep: a common term for nonrapid eye movement sleep stages 3 and 4 (also called delta or slow wave sleep)

Entrainment: synchronization of a biologic rhythm by a forcing stimulus such as an environmental time cue (zeitgeber)

Excessive daytime sleepiness: difficulty in maintaining the alert-awake state usually accompanied by a rapid entrance into sleep when the person is sedentary; results in somnolence and hypersomnia

Insomnia: difficulty in initiating or maintaining sleep

NREM sleep: nonrapid eye movement sleep divided into four stages (1–4)

Periodic limb movement: a rapid partial flexion of the foot at the ankle, extension of the big toe, and partial flexion of the knee and hip that occurs during sleep; the movements occur with a periodicity of 5–90 seconds and last 0.5–5.0 seconds.

Periodic limb movement disorder: a disorder characterized by periodic episodes of repetitive and highly stereotyped limb movements that occur during sleep

REM sleep: rapid eye movement sleep

Sleep apnea syndrome: a disorder characterized by repetitive episodes of reduced or absent respiratory airflow that occur during sleep and that usually are associated with a reduction in blood oxygen level

Sleep architecture: the NREM-REM sleep stage and cycles

Sleep efficiency: the proportion of sleep in the episode filled by sleep; the ratio of total sleep time to time in bed

Sleep hygiene: the conditions and practices that promote continuous and effective sleep

Sleep latency: time from lights out to the onset of sleep defined as the first of three consecutive epochs of stage 1 sleep or the first epoch of any other stage of sleep

Total sleep time: the amount of actual sleep time in a sleep episode; the time is equal to the total sleep episode less the awake time.

Zeitgeber: an environmental time cue, such as sunlight, noise, social interaction, or an alarm, that usually helps an individual entrain to the 24-hour day

Figure 2. Sleep-Related Terms and Definitions

Note. Based on information from American Academy of Sleep Medicine, 2001.

Mullaney, & Gillan, 1992; Jean-Louis et al., 1996). Correlations decrease when sleep is disturbed or activity is decreased (Pollack, Tryon, Nagaraja, & Dzwonczyk, 2001; Sadeh, Hauri, Kripke, & Lavie, 1995).

Sleep can be studied through subjective assessments of sleep latency (i.e., time from turning the light out to the onset of sleep), number of awakenings, depth and length of sleep, refreshing quality of sleep, satisfaction with sleep, and soundness of sleep (Spielman, Yang, & Glovinsky, 2000). This type of information can be collected through the use of sleep questionnaires, sleep diaries, visual analog scales, and interviews (Shaver & Giblin, 1989). Instruments and questionnaires available for these assessments are summarized in Table 1. Subjective assessments of sleep quality frequently, but not always, correlate with the objective data obtained

through polysomnography (Baekland & Hoy, 1971; Ton et al., 1988).

Sleep Disorders

Sleep disorders include an array of problems that are characterized by insomnia, excessive daytime sleepiness, or abnormal movements, behaviors, or sensations during sleep. Three primary groups of sleep disorders are outlined in the International Classification of Sleep Disorders (American Academy of Sleep Medicine, 2001) (see Figure 3). Dyssomnias are those disorders that produce difficulty initiating or maintaining sleep or excessive sleepiness. Dyssomnias may be related to intrinsic factors (e.g., idiopathic insomnia, obstructive sleep apnea, periodic limb movements), extrinsic factors (e.g., medications, environmental conditions), or circadian rhythm factors

Table 1. Instruments for Subjective Assessment of Sleep and Daytime Sleepiness

Instrument	Format	Distinctions	Parameters Assessed
Sleep Quality Questionnaires			
Leed's Sleep Evaluation Questionnaire (Parrot & Hindmarch, 1980)	Visual analog scales	10 items; used specifically to assess responses to pharmacologic agents	Sleep latency, sleep quality, and daytime alertness
Pittsburgh Sleep Quality Index (Buysse et al., 1989)	Fill-in-the-blank statements and frequency and severity ratings	24 items; has a section for bed partner ratings in addition to self-rated parameters; provides composite global sleep quality score	Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication, and daytime dysfunction
Sleep Impairment Index (Morin, 1993)	Frequency and severity ratings	15 items; specific to insomnia	Sleep quality, daytime function, sleep disturbance, and etiologic factors
St. Mary's Hospital Sleep Questionnaire (Ellis et al., 1981)	Fill-in-the-blank statements and frequency and severity ratings	14 items; designed for use with inpatients	Subjective sleep quality, sleep latency, sleep duration, sleep disturbance, and daytime alertness
Sleep History Questionnaire			
Sleep Questionnaire and Assessment of Wakefulness (Miles, 1982)	Yes or no questions, severity and frequency ratings, and fill-in-the-blank statements	863 items	Sleep quality; habitual nocturnal and daytime sleep patterns; sleep-related symptoms; etiologic factors; daytime functioning; physical, emotional, and social assessment; personal and family medical history; and medication and substance use
Sleep Diaries			
National Sleep Foundation Sleep Diary (National Sleep Foundation, 1999)	Fill-in-the-blank statements	Table format allows for comparison of multiple days on one page.	Night-to-night sleep patterns, sleep quality, and daily practices that affect sleep (e.g., activity, naps, medications, caffeine)
Pittsburgh Sleep Diary (Monk et al., 1994)	Fill-in-the-blank statements, frequency ratings, and visual analog scales	24 items per day, one page per day	Night-to-night sleep patterns, sleep quality, and daily practices that affect sleep (e.g., activity, naps, medications, caffeine)
Sleep Log (Spielman & Glovinsky, 1997)	Fill-in-the-blank statements and severity ratings	Graphical format; seven days on one page	Night-to-night sleep patterns, sleep quality, and daily practices that affect sleep (e.g., activity, naps, medications, caffeine)
Daytime Sleepiness Inventories			
Epworth Sleepiness Scale (Johns, 1991)	Rating scale	Eight items; yields sleepiness score	Likelihood of falling asleep in hypothetical situations
Functional Outcomes of Sleep Questionnaire (Weaver et al., 1997)	Severity scale and fill-in-the-blank statements	30 items; assesses the impact of sleepiness on multiple activities of daily living	Activity level, vigilance, intimacy and sexual relationships, general productivity, and social outcome
Stanford Sleepiness Scale (Hoddes et al., 1973)	Rating scale	Seven points related to level of alertness or sleepiness	Introspective sleepiness

Dyssomnias

- Intrinsic sleep disorders
 - Psychophysiologic insomnia
 - Sleep state misperception
 - Idiopathic insomnia
 - Narcolepsy
 - Recurrent hypersomnia
 - Idiopathic insomnia
 - Obstructive sleep apnea syndrome
 - Central sleep apnea syndrome
 - Central alveolar hypoventilation syndrome
 - Periodic limb movement disorder
 - Restless legs syndrome
 - Intrinsic sleep disorder NOS
- Extrinsic sleep disorders
 - Inadequate sleep hygiene
 - Environmental sleep disorder
 - Altitude insomnia
 - Adjustment sleep disorder
 - Insufficient sleep syndrome
 - Limit-setting sleep disorder
 - Sleep-onset association disorder
 - Food allergy insomnia
 - Nocturnal eating (or drinking) syndrome
 - Hypnotic-dependent sleep
 - Stimulant-dependent sleep disorder
 - Alcohol-dependent sleep disorder
 - Toxin-induced sleep disorder
 - Extrinsic sleep disorder NOS
- Circadian rhythm sleep disorders
 - Time zone change (jet lag) syndrome
 - Shift-work sleep disorder
 - Irregular sleep-wake pattern
 - Delayed sleep phase syndrome
 - Advanced sleep phase syndrome
 - Non-24-hour sleep-wake disorder
 - Circadian rhythm sleep disorder NOS

Parasomnias

- Arousal disorders
 - Confusional arousals
 - Sleepwalking
 - Sleep terrors
- Sleep-wake transition disorders
 - Rhythmic movement disorder
 - Sleep starts
 - Sleep-talking
 - Nocturnal leg cramps
- Parasomnias usually associated with REM sleep
 - Nightmares
 - Sleep paralysis
 - Impaired sleep-related penile erections

- Sleep-related painful erections
 - REM sleep-related sinus arrest
 - REM sleep behavior disorder
- Other parasomnias
 - Sleep bruxism
 - Sleep enuresis
 - Sleep-related abnormal swallowing syndrome
 - Nocturnal paroxysmal dystonia
 - Sudden unexplained nocturnal death syndrome
 - Primary snoring
 - Infant sleep apnea
 - Congenital central hypoventilation syndrome
 - Sudden infant death syndrome
 - Benign neonatal sleep myoclonus
 - Other parasomnia NOS

Disorders Associated With Medical or Psychiatric Disorders

- Mental disorders
 - Psychoses
 - Mood disorders
 - Anxiety disorders
 - Panic disorders
 - Alcoholism
- Neurologic disorders
 - Cerebral degenerative disorders
 - Dementia
 - Parkinsonism
 - Fatal familial insomnia
 - Sleep-related epilepsy
 - Electrical status epilepticus of sleep
 - Sleep-related headaches
- Other medical disorders
 - Sleep sickness
 - Nocturnal cardiac ischemia
 - Chronic obstructive pulmonary disease
 - Sleep-related asthma
 - Sleep-related gastroesophageal reflux
 - Peptic ulcer disease
 - Fibromyalgia

Proposed Sleep Disorders

- Short sleeper
- Long sleeper
- Subwakeful syndrome
- Fragmentarily myoclonus
- Sleep hyperhidrosis
- Menstual-associated sleep disorder
- Pregnancy-associated sleep disorder
- Sleep-choking syndrome
- Terrifying hypnagogic hallucinations
- Sleep-related neurogenic tachypnea
- Sleep-related laryngospasm

NOS—not otherwise specified; REM—rapid eye movement

Figure 3. Common Sleep Disorders

Note. Based on information from American Academy of Sleep Medicine, 2001.

(e.g., shift work, irregular sleep-wake pattern, advanced or delayed sleep phase). Parasomnias include abnormal behaviors or sensations during sleep, such as nightmares, sleep walking, and bruxism. The third category includes sleep disorders associated with medical or psychiatric disorders, such as Parkinson disease, sleep-related epilepsy, and mood disorders.

A category of proposed sleep disorders includes conditions for which only limited evidence of their existence is available.

Excessive daytime sleepiness (i.e., the inability to maintain the alert-awake state) is the most common consequence of sleep disorders and insufficient or poor sleep and is the most

common complaint of patients seen in sleep disorder centers in the United States. However, because of the often vague and nonspecific clinical presentation, the condition frequently is unrecognized by healthcare providers in other clinical settings (El-Ad & Korczyn, 1998; Roehrs, Carskadon, Dement, & Roth, 2000). Patients may have little insight into the nature and severity of the problem or the negative effects that excessive daytime sleepiness has on their lives. In milder forms, excessive daytime sleepiness may cause only minor decrements in social and occupational functioning (American Academy of Sleep Medicine, 2001). When severe, however, the condition can be debilitating, causing a broad range of neuropsychological deficits affecting daytime functioning and quality of life. Daytime sleepiness can be life threatening because of associated alterations in alertness and reactivity (Bedard, Montplaisir, Richer, Rouleau, & Malo, 1991; Bliwise, 1989; Briones et al., 1996; Dinges, 1989). Although poor sleep can cause excessive daytime sleepiness, abnormal daytime sleepiness also can affect nocturnal sleep adversely. Thus, a complete assessment of sleep should examine nocturnal and daytime sleep-wake patterns.

Disturbed Sleep in Patients With Cancer

The Regulation of Sleeping and Waking

The Two-Process Model of Sleep Regulation provides a framework for understanding how cancer, cancer treatment, and associated patient responses may affect sleeping and waking (Borbely & Achermann, 2000). According to this model, the major mechanisms controlling sleep and waking are (a) a homeostatic process determined by prior sleep and waking and (b) a circadian process that designates periods of high and low sleep propensity. The homeostatic process reflects the physiologic need for sleep, which builds across the day and dissipates throughout the night. A key indicator of this process is EEG slow wave activity, which is high during the beginning of a sleep episode but declines as the night progresses. A biologic oscillator (located in the suprachiasmatic nucleus) controls the circadian process, a sinusoidal rhythm of approximately 24 hours. The circadian process regulates sleep propensity, and its effects are greatest in the early morning hours. The rhythm of core body temperature is a key indicator of the circadian process. The timing and duration of sleep are determined by the combined action of homeostatic and circadian processes via their influence on thermoregulatory and neuronal or neurohormonal systems (Borbely & Achermann; Van Someren, 2000). Factors that oppose or enhance these processes can have significant effects on the timing, duration, and structure of sleep as well as daytime alertness.

Factors Potentially Contributing to Sleep Disturbance

Patients with cancer are at high risk for sleep disturbances because of a number of factors that may alter normal sleep regulatory processes such as demographic, lifestyle, psychological, and disease- and treatment-related variables (see Figure 4).

Demographic factors: Older age, female gender, and Caucasian race all have been associated with increased reports of sleep problems (Blazer, Hays, & Foley, 1995; Bliwise, 2000; Rediehs, Reis, & Creason, 1990). Of these factors, age appears to have the most significant impact. The increased fragmentation of sleep, decreased amount of deep sleep, and increased

Demographic Factors

- Older age
- Gender
- Race

Disease-Related Factors

- Pain
- Activity-rest
- Hormone secretion
- Cytokine production

Lifestyle Factors

- Poor sleep hygiene
- Caffeine intake
- Alcohol intake
- Smoking

Psychological Factors

- Depression
- Anxiety
- Worry or stress

Treatment-Related Factors

- Chemotherapy
- Biotherapy
- Radiotherapy
- Medication use

Figure 4. Factors Contributing to Sleep Disturbance in Patients With Cancer

daytime napping seen in the elderly are linked to age-related changes that alter homeostatic and circadian processes, including (a) nocturia, (b) elevated autonomic activity that results in a greater susceptibility to arousal, and (c) decreased strength of circadian rhythms (Bliwise, 2000). Furthermore, primary sleep disorders such as sleep apnea (Ancoli-Israel et al., 1991), periodic limb movements during sleep (Montplaisir, Nicolas, Godbout, & Walters, 2000), and insomnia are more prevalent in the elderly (Zorick & Walsh, 2000). Although older men have more objective changes in sleep architecture, older women are more likely to complain of sleep difficulties (Rediehs et al.). Because 76% of all cancer diagnoses occur in patients aged 55 or older (American Cancer Society, 2004), the majority of patients with cancer may be at risk for sleep problems related to age.

Lifestyle factors: Lifestyle factors, such as the timing and duration of the nocturnal sleep period and exposure to environmental stimuli, may disturb sleep by adversely interacting with sleep regulatory processes (Zarcone, 2000). For example, because the homeostatic drive for sleep is influenced by the amount of prior sleeping or waking, daytime napping can influence nighttime sleep (Monk, Buysse, Carrier, Billy, & Rose, 2001). Long naps taken during the daytime hours, especially late in the day, decrease the propensity to sleep during the nocturnal sleep period. In addition, irregular bedtimes, staying in bed longer, and decreased daytime activity interfere with circadian activity rest patterns (Roehrs, Zorick, & Roth, 2000). Thus, maintenance of regular bed and rise times and patterns of daily activity is important. Room temperature, noise, and light level also can interfere with sleep onset or continuity (Aldrich, 1999). Likewise, consuming caffeine in coffee and soft drinks, smoking, and drinking alcohol interfere with sleep by producing arousal responses. Caffeine may disrupt sleep by blocking the sleep-enhancing factor adenosine (Phillis & Wu, 1982), whereas nicotine may act as a central nervous system stimulant (Soldatos, Kales, Scharf, Bixler, & Kales, 1980). Although alcohol ingestion initially is associated with sedation, falling blood alcohol levels produce sympathetic arousal, disturbing sleep continuity later in the night (Zarcone, 2000).

Psychological factors: Some sleep disturbances in patients with cancer may be related to psychological factors (Hu & Silberfarb, 1991; Savard & Morin, 2001). Difficulty sleeping may follow stressful life events, such as a cancer diagnosis,

that produce worry or concern regarding the disease, treatment, or impact on family members (Roehrs, Zorick, et al., 2000). Depression and anxiety, the most common psychiatric disorders in patients with cancer (Bottomley, 1998; Derogatis et al., 1983; van't Spijker, Trijsburg, & Duivenvoorden, 1997), also are known to affect sleep. Changes in sleep architecture (e.g., decreases in slow wave sleep, short REM latency, increased REM percentage) often are seen in depression (Aldrich, 1999; Benca, 2000) and may be caused by abnormalities in sleep homeostatic (Borbely & Wirz-Justice, 1983) and circadian processes (Avery, Wildschiodtz, Smallwood, Martin, & Rafaelsen, 1986; Schultz & Lund, 1983). Similarly, anxiety and worry can interfere with the homeostatic process by causing increased physiologic arousal resulting in increased sleep latency, increased number of awakenings, and decreased slow wave sleep (Reynolds, Shaw, Newton, Coble, & Kupfer, 1983). However, documentation of a causal relationship among depression, anxiety, and sleep disturbances is clouded by data indicating that sleep problems can precede the development of these psychological problems (Breslau, Roth, Rosenthal, & Andreski, 1996; Ford & Kamerow, 1989) or precipitate changes in mood (Bonnet, 1985; Friedman, Globus, & Huntley, 1977).

Disease-related factors: Patients with cancer experience multiple conditions associated with the disease, including pain, altered activity and rest patterns, altered hormone secretion, and cytokine production, that may affect sleeping and waking.

Pain: Sleep may be affected by pain, which is experienced by up to 80% of patients with cancer (Cleeland et al., 1994; Higginson & Hearn, 1997; Vainio & Auvinen, 1996). The significant impact of pain on sleep is highlighted by data revealing that (a) 30%–60% of patients in pain complain of sleep difficulty (Dorrepaal, Aaronson, & van Dam, 1988; Portenoy et al., 1991; Ripamonti et al., 2000; Strang, 1992; Strang & Qvarner, 1990), (b) the intensity of cancer pain relates inversely to total sleep time (Tamburini, Selmi, DeConno, & Ventafridda, 1987), and (c) adequate control of pain results in a significant reduction in the occurrence and severity of insomnia (Meuser et al., 2001).

Animal (Carli, Montesano, Rapezzi, & Paluffi, 1987; Landis, Levine, & Robinson, 1989) and human studies (Drewes, Nielsen, Arendt-Nielsen, Birket-Smith, & Hansen, 1997) indicate that pain produces a persistent arousal state that interferes with sleep homeostatic processes. However, the precise mechanisms by which acute and chronic pain syndromes may affect the sleep of patients with cancer remain to be described. Furthermore, given that psychological processes can influence the expression and experience of pain, significant and complex interactions among pain, depression or anxiety, and sleep may exist. For example, pain has been associated positively with depression (Derogatis et al., 1983; Portenoy et al., 1991; Strang, 1992; Strang & Qvarner, 1990), whereas sleep loss has been associated with decreased pain thresholds and somatic complaints (Dinges et al., 1997; Hicks, Coleman, Ferrante, Sahatjian, & Hawkins, 1979; Lenz, Landis, Rothermel, & Shaver, 1999; Moldofsky & Scarisbrick, 1976). Totterdell, Reynolds, Parkinson, and Briner (1994) found that sleep quality was more likely to predict the following day's mood and physical symptoms than were mood and symptoms able to predict the following night's sleep quality. Similarly, patients have reported that sleep decreased their pain (Donovan,

Dillon, & McGuire, 1987) and experimental administration of delta sleep-inducing peptide, a naturally occurring neuropeptide that induces deep sleep, reduced pain and symptoms of depression (Larbig, Gerber, Kluck, & Schoenenberger, 1984).

Activity-rest: Activity, social interaction, and adequate light exposure have been found to be important in the promotion of sleep quantity and quality (Naylor et al., 2000; Ohayon, Zulley, Guilleminault, Smirne, & Priest, 2001; Okawa et al., 1991). Environmental cues, known as zeitgebers, help to synchronize or entrain the internal biologic clock with the 24-hour day. This is analogous to setting the body clock to local time, which promotes consolidated nocturnal sleep periods. However, several studies have described disrupted circadian activity and rest cycles (e.g., low activity, less consolidation of higher daytime and lower nighttime activity) in patients with cancer (Berger & Farr, 1999; Berger & Higginbotham, 2000; Mormont et al., 2000). Under these circumstances, patients with cancer may have decreased exposure to light (the strongest zeitgeber) as well as other important synchronizing clues such as regular meals, periods of activity, and social interactions (Klerman et al., 1998). Furthermore, irregular sleeping patterns (e.g., shortened nocturnal sleep and frequent daytime napping experienced by many patients with cancer) also may interfere with the homeostatic process because an episode of prior waking is too short to generate propensity for sleep (Campbell & Zulley, 1989).

Hormone secretion: Studies have shown that patients with cancer exhibit blunted or erratic circadian patterns of cortisol (Payer et al., 1997; Sephton, Sapolsky, & Kraemer, 2000; Touitou, Bogdan, Benavides, & Auzey, 1996; Touitou et al., 1995) and melatonin production (Bartsch, Bartsch, Fluchter, Attanasio, & Gupta, 1985; Bartsch, Bartsch, Schmidt, Bichler, & Fluchter, 1992; Bartsch et al., 1989). Because secretion of these hormones is governed primarily by circadian factors, these changes may indicate a disruption of normal circadian processes (Van Cauter, 2000). Alterations in circadian rhythms can result in shortened, irregular sleep periods and excessive daytime sleepiness (Bliwise, 1999; Cohen & Albers, 1991; Myers & Badia, 1995). However, sleep-wake transitions also have been shown to modulate secretion of cortisol; therefore, flattened or erratic cortisol rhythms may be an indication of altered sleep (Follenius, Brandenberger, Bandesapt, Libert, & Ehrhart, 1992; Spath-Schwalbe, Gofferje, Kern, Born, & Fehm, 1991). Melatonin has been found to have a role in the regulation of body temperature (Cagnacci, Elliott, & Yen, 1992) and sleep (Shocat, Luboshitzky, & Lavie, 1997). In addition to circadian factors, melatonin secretion is regulated by exposure to light (Czeisler & Khalsa, 2000). Elderly patients living in conditions of insufficient environmental light reportedly have low melatonin levels along with sleep difficulties (Mishma, Okawa, Shimizu, & Hishikawa, 2001). Supplementation with bright light improved melatonin secretion and sleep quality, suggesting that light therapy may improve the sleep of patients with cancer who have attenuated environmental exposure.

Cytokine production: Cytokines are polypeptides that are important in neural and immune system function as well as regulation of numerous cell and tissue functions (Benca & Quintans, 1997; Rothwell, 1993). Evidence exists that peripherally produced cytokines can affect the central nervous system through transport mechanisms that permit their passage

into brain tissue through the blood-brain barrier (Banks, Kastin, & Broadwell, 1995), by vagal nerve stimulation (Ericsson, Kovacs, & Sawchenko, 1994), and by entry through gaps in the blood-brain barrier (Meyers & Valentine, 1995). Cytokines also are thought to play a key role in the clinical effects of medical disease (Reichenberg et al., 2001), including thermoregulatory factors (circadian process) related to sleep regulation. Cytokines (e.g., IL-1, IL-6, TNF- α) induce fever through release of prostaglandin E2 (Dinarello & Bunn, 1997). Cytokines also stimulate synthesis and release of corticotropin-releasing factor in the hypothalamus that ultimately affects both skin and core body temperature, which impacts sleep-wake states, through sympathetic nervous system regulation and increased peripheral metabolism (Rothwell).

Cancer cells produce and induce production of cytokines (Ardestani, Inserra, Solkoff, & Watson, 1999), and elevated levels of cytokines (e.g., IL-1, IL-6, TNF- α) have been found in the blood, ascites, pleural effusions, and urine of patients with cancer (Dunlop & Campbell, 2000). Daytime sleepiness and longer sleep times seen in some patients with cancer may be an exaggeration of the physiologic effects of IL-1 and TNF- α that promote NREM sleep (Krueger et al., 1995). Cytokines also have been implicated in clinical depression and mood changes (e.g., anxiety) in patients with cancer, which may provide some explanation for the high co-occurrence of these symptoms with sleep disturbance (Holden, Pakula, & Mooney, 1998; Musselman et al., 2001; Reichenberg et al., 2001).

Treatment-related factors: Patients with cancer receive multiple therapeutic modalities aimed at controlling the disease process or concurrent symptoms. These modalities, including chemotherapy, biotherapy, radiotherapy, and medications, can affect sleep regulation.

Chemotherapy: Sleep problems have been reported in patients undergoing chemotherapy (Berger & Farr, 1999; Berger & Higginbotham, 2000; Broeckel, Jacobsen, Horton, Balducci, & Lyman, 1998; Redecker, Lev, & Ruggiero, 2000). Objective measures of sleep in patients undergoing chemotherapy along with detailed descriptions of clinical correlates are very limited. Therefore, the direct or indirect effects of chemotherapy agents on sleep are unknown. However, menopausal symptoms arising from chemotherapy and hormonal therapy (i.e., tamoxifen), especially those of a vasomotor type (e.g., hot flashes, sweating), have been related to sleep disturbance (Broeckel et al.; Couzi, Helzlsouer, & Fetting, 1995; Mourits et al., 2001; Stein, Jacobsen, Hann, Greenberg, & Lyman, 2000). Nocturnal hot flashes, occurring in 48% of patients with breast cancer (Carpenter, Shiva, Freedman, & Andrykowski, 2001), have been associated with nocturnal restlessness and awakenings (Polo-Kantola, Erkkola, Helenius, Irjala, & Polo, 1998; Stein et al.) that may interfere with sleep homeostasis. In addition, estrogen may be involved in thermoregulatory processes (Empson & Purdie, 1999). The circadian rhythm of hot flashes is different in women with breast cancer as opposed to healthy postmenopausal women, implying an alteration in the circadian process that may have further implications for sleep disturbance (Carpenter et al.).

Biotherapy: Cytokines, a diverse group of peptide molecules that regulate cell and tissue functions, sometimes are used to treat cancer or used as adjuncts to chemotherapy or ra-

diotherapy (Dunlop & Campbell, 2000). These biologic agents, especially interferon, IL-2, and TNF- α , are associated with a variety of side effects, including daytime sleepiness, disturbed sleep, and depression (Capuron, Ravaud, & Dantzer, 2000; Valentine, Meyers, Kling, Richelson, & Hauser, 1998). These agents have the potential to interfere with sleep homeostatic and circadian processes.

Radiotherapy: Patients undergoing radiotherapy have reported problems with nocturnal sleep and daytime sleepiness (Beszterczey & Lipowski, 1977; Faithfull, 1991; Miaskowski & Lee, 1999). Although little investigation has occurred related to the mechanisms by which radiotherapy may interfere with sleep and wakefulness, researchers have hypothesized that alterations in cytokine expression may be an important factor (Belka, Budach, Kortman, & Bamberg, 2001; Greenberg, Gray, Mannix, Eisenthal, & Carey, 1993). In particular, Greenberg et al. found that serum IL-1 levels in patients

Table 3. Drugs With Sleep-Impairing Properties

Category	Drug	Effect
Analgesics	Opioids	↓ REM sleep, ↓ stage II, ↓ arousal
	Nonsteroidal anti-inflammatory drugs (e.g., aspirin, ibuprofen, naproxen)	↑ stage II, ↓ SWS, altered thermoregulation
Antidepressants	Tricyclic drugs (e.g., amitriptyline, doxepin, imipramine, trimipramine, desipramine, nortriptyline)	↓ REM sleep, ↑ TST
	Selective serotonin reuptake inhibitors (e.g., fluoxetine, paroxetine, fluvoxamine)	↓ REM sleep, ↓ TST
Antiemetics	Dopamine antagonists (e.g., phenothiazines, metoclopramide)	Drowsiness, sedation, ↓ REM sleep
	Anticholinergic agents (e.g., scopolamine)	Delayed REM onset, ↓ REM sleep, ↑ stage II, ↑ body movement
	5-HT ₃ antagonists (e.g., ondansetron, granisetron)	Drowsiness
Anxiolytics	Benzodiazepines (e.g., alprazolam, diazepam, lorazepam)	↓ SWS and REM sleep, ↑ stage II, shortened REM latency, altered thermoregulation
Corticosteroids	Prednisone and dexamethasone	Insomnia, bad dreams
Hypnotics	Benzodiazepines (e.g., flurazepam, triazolam, temazepam)	↓ SWS and REM sleep (mild), altered thermoregulation
	Nonbenzodiazepines (e.g., zaleplon, zolpidem, zopiclone)	Minimal to no effect on SWS and REM, ↓ sleep latency

REM—rapid eye movement; SWS—slow wake sleep; TST—total sleep time
Note. Based on information from Dietrich, 1997; Kay & Samiuddin, 1988; Nicholson et al., 1994; Schweitzer, 2000.

receiving radiotherapy increased during the first four weeks of treatment and that, at least for some subjects, hours slept and serum IL-1 levels were significantly correlated.

Medication use: Many medications used by patients with cancer affect sleep. Patients receive a wide variety of pharmacologic agents to treat the disease process and manage or control multiple symptoms. Many of these agents are associated with sleep-wake disturbances or changes in sleep architecture. The major classes of drugs used for symptom management and their effects on sleep and wakefulness are summarized in Table 3.

Summary

Adequate quantity and quality of sleep are important for functioning and well-being. A good night of sleep can provide respite and renewal for patients with cancer and may enhance

energy and coping. Unfortunately, many nurses, as well as the patients they serve, do not have an adequate understanding of sleep and the impact of nocturnal sleep disturbance and excessive daytime sleepiness on functioning and quality of life. In patients with cancer, numerous complex and interacting factors have the potential to generate sleep-wake disturbances through altered sleep regulatory processes. An understanding of normal sleep, sleep pathology, and the factors that can precipitate sleep disturbance provides a context for nurses to interpret sleep complaints in their patients, evaluate responses to sleep promoting interventions, and guide decision making regarding referrals.

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Continuing education (CE) credit for this article has been combined with its companion article, “Sleep-Wake Disturbances in People With Cancer Part II: Evaluating the Evidence for Clinical Decision Making” (see next page).

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